A Dissertation on

A STUDY ON NEUROLOGICAL MANIFESTATIONS OF HIV WITH REGARD TO CD4 COUNT

Dissertation Submitted to

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY

CHENNAI - 600 032

With partial fulfillment of the regulations
for the award of the degree of

M.D. GENERAL MEDICINE

BRANCH-I

COIMBATORE MEDICAL COLLEGE,
COIMBATORE
APRIL 2015

CERTIFICATE

Certified that this is the bonafide dissertation done by **Dr. SREEDEVI S** and submitted in partial fulfillment of the requirements for the Degree of **M.D., General Medicine**, Branch I of**TheTamilnaduDr. M.G.R. Medical University, Chennai.**

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Date: **Professor & Head**

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I solemnly declare that the dissertation titled **"A STUDY ON NEUROLOGICAL MANIFESTATIONS OF HIV WITH REGARD TO CD4 COUNT"** was done by me from AUGUST 2013 to JULY 2014 at Coimbatore Medical College hospital under the guidance and supervision of Professor **Dr. S. USHA .M.D.**

This dissertation is submitted to **The Tamilnadu Dr. M.G.R. Medical University towards** the partial fulfilment of the requirement for the award of MD Degree in General Medicine(Branch I).

Place: Coimbatore **DR SREEDEVI S**

Date

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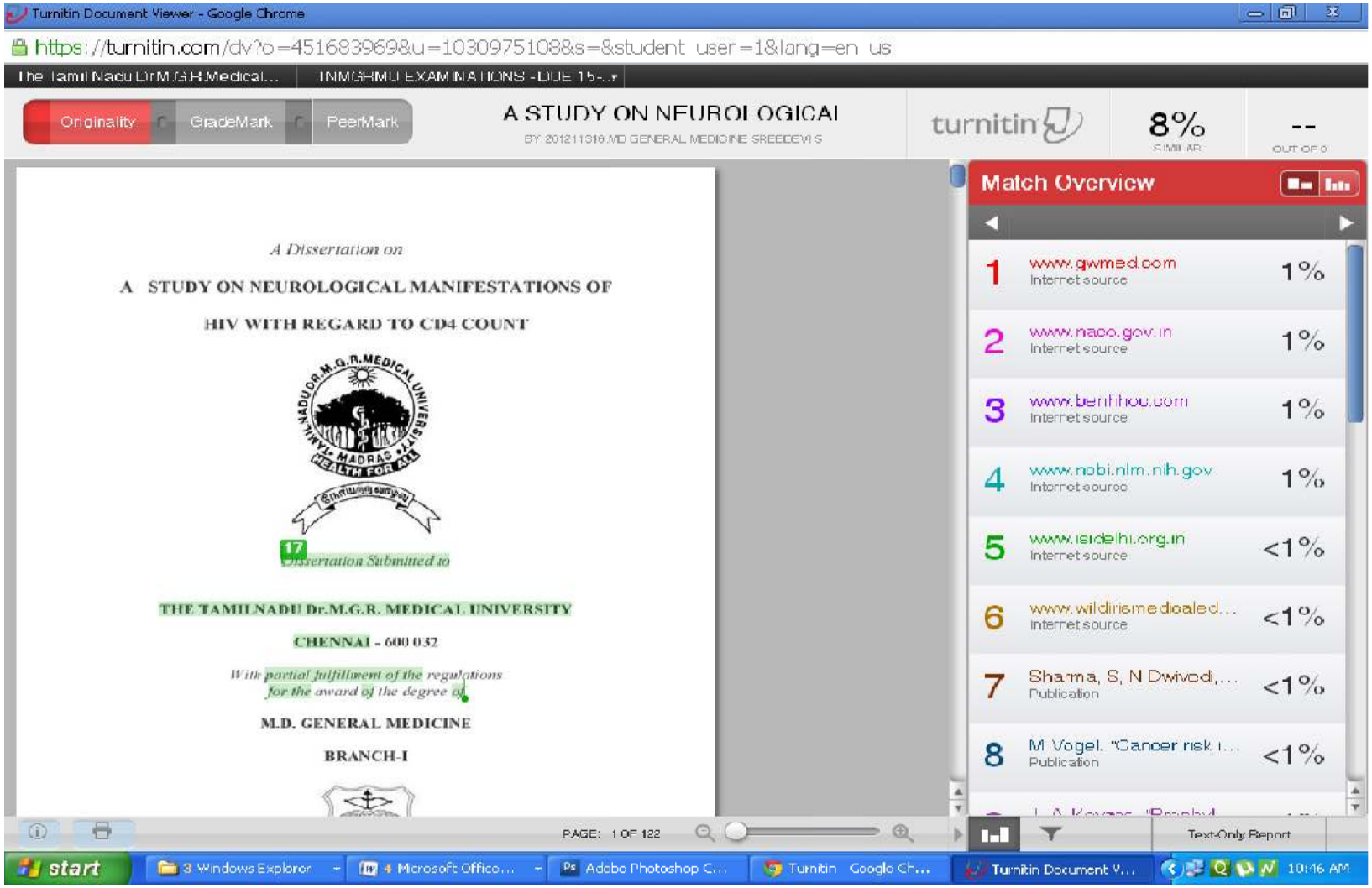
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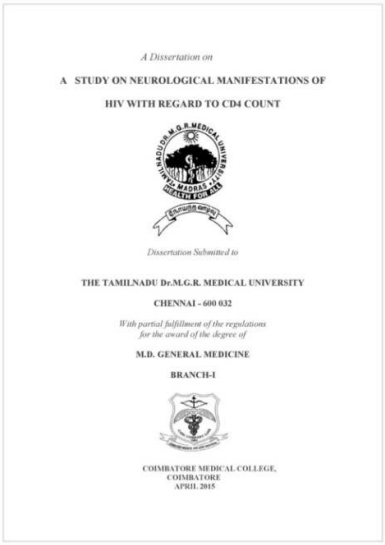

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LIST OF ABBREVIATIONS USED

AIDS	-	Acquired Immunodeficiency Syndrome
HIV	-	Human Immunodeficiency Virus
CD4	-	Cluster Differentiation Factor 4
ELISA	-	Enzyme Linked Immunosorbent Assay
CNS	-	Central Nervous System
PP	-	Progressive Polyradiculopathy
IDP	-	Inflammatory Demyelinating Polyneuropathy
PCNSL	-	Primary Central Nervous System Lymphoma
PML	-	Progressive Multifocal Leucoencephalopathy
EMG	-	Electromyography
NMDA	-	N-Methyl-D-Aspartate
CVA	-	Cerebrovascular Accident
CSF	-	Cerebrospinal Fluid
VIP	-	Vasopressin Inhibitory Peptide
CK	-	Creatine Kinase
IL	-	Interleukin
TNF	-	Tumour Necrosis Factor
IFN	-	Interferon
PCR	-	Polymerase Chain Reaction
STD	-	Sexually Transmitted Disease

PCP	-	Pneumocystis Carinii
GP	-	Glycoprotein
ART	-	Antiretroviral Therapy
VDRL	-	Venereal Disease Research Laboratory
RNA	-	Ribocucleic Acid
DNA	-	DeoxyRibocucleic Acid
MHC	-	Main Histocompatibility Complex
CMV	-	Cytomegalovirus
CSW	-	Community Sex Worker

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ABSTRACT

Background and Objectives

HIV/AIDS has posed many unprecedented challenges. It causes a white spectrum of disease manifestation. Approximately 60 % of the AIDS patients have neurological symptoms and 80-90 % is found to have neuro-pathological abnormality at biopsy. The pattern of neurological complication in HIV infection in India is different from that of western countries. This study was under taken to 1-Study the neurological manifestations in HIV patients admitted in to CMC Hospital, Coimbatore 2-to note differences with various studies carried out in other parts of the world.

Methods

Patents admitted in CMC Hospital, Coimbatore between August 2013 to August 2014 with symptoms referring to nervous system were screened and confirmed to have HIV-1 and/or HIV-2 infection (seropositive) by ICTC (Trispottest,Trilenetest,Dot immunoassay)were enrolled if they met the inclusion criteria.

RESULTS

74 of the 672 HIV positive patients fulfilled the inclusion criteria and were studied for neurological manifestations (>11 %). 51 were males and 23females with F:M ratio 1:2.2 and mean age ranged from 21-51 years. Majority of the patients were in economically productive age group. 61% were presenting with neurological symptoms and signs for the first time and were diagnosed HIV positive following admission.

Tuberculosis is the single most common organism affecting CNS(64%.) Headache, fever and altered sensorium were commonest symptoms in HIV patients with Neurological pathology.

CD4 count less than 200 was seen in 24 of these patients(32%).others above 200 but below 500.so there is strong association between development of opportunistic infection and CD4 count.

As compared to western literature CNS TB was the commonest disease associated with HIV infections in our study. It was presenting pathology in 68% of the cases. It was associated with Pulmonary TB in 10% the cases. 23patients showed Space occupying lesion. Mean CD4 Count observed to be 210.7

Interpretation and Conclusion

There is high incidence of neurological manifestations with tuberculosis and Toxoplasmosis being commonest pathogenic agents in course of HIV infections in this study. Simple investigations like CD4 count may provide a clue to the degree of underlying immunosuppression and indicate the need to start ART in HIV/AIDS patients.

Key words

Human Immunodeficiency Virus; Tubercular meningitis; Cryptococcal meningitis; bacterial meningitis; Tuberculoma; CD4 count.

INTRODUCTION

AIDS was first recognized in the United States in 1981[01]. In India it was first pointed out in 1986 in Tamil Nadu.

The HIV/AIDS has posed many challenges. Like the tip of the ice and real magnitude of iceberg remains under sea, the real magnitude of HIV and AIDS still remains to be evaluated.

HIV and AIDS cause a wide spectrum of diseases and manifestations. Approximately 60 percent of patients with AIDS have neurological symptoms and 80 to 90 percent were found to have neuropathological abnormalities in autopsy[3]. Neurological complications of HIV infection cause marked morbidity and are often associated with high mortality. The pattern of presentation in India appears to differ from the world literature in that TB meningitis leads the list of opportunistic neurological infections.

AIMS & OBJECTIVES

1) To study various Neurological manifestations of HIV infection in patients presenting to the general medicine department at Government Headquarters hospital, Coimbatore with reference to the patient's CD4 count.

2) To note the gross and subtle differences in the Neurological manifestations of HIV infection in patients in this study with the various studies carried out in other countries.

REVIEW OF LITERATURE

EPIDEMIOLOGY OF HIV/AIDS

Historical Milestones

- First recognized in the United States in 1981.

- In 1981 Pneumocystis carinii pneumonia (PCP) was reported in 5 homosexual men in Los Angeles and of Kaposi's sarcoma in 26 homosexual men in 2 cities of US Viz. New York and Los Angeles.[1]

- Both were reported by US Centre for Disease Control and Prevention.

- Indication that the disease is caused by a retrovirus came first in 1983 from French scientists, when professor Montagnier and his co-worker isolated the causative viral agent, which was later named as Human immunodeficiency virus (HIV).

- ELISA technique to detect the presence of antibodies in blood against HIV was developed in 1984.

- In 1986, the Montagnier's group discovered a new type of HIV in West Africa and labeled it as HIV-2.

- In 1987,for the first time Zidovudine was reported to be useful in managing the patient with HIV infection for the first time.

The Global Scenario[6]

- A global pandemic
- Al countries have reported HIV cases

The Indian Scenario[5]

- HIV/AIDS in India was first detected in 1986 in Chennai,Tamilnadu and later from Mumbai in 1987.
- Presence of HIV-2 infection in India was reported for the first time from Mumbai in 1991.[8]
- India is said to have the lowest population with HIV[10], though it has the third largest number of people living with HIV/AIDS. Based on HIV Sentinel Surveillance 2008, it is estimated that India has an adult prevalence of 0.31 percent[2] with 23.9 lakh people infected with HIV, of which, 39 percent(9.3 lakhs) are female and 3.5 percent are children. , while 83 percent are the in age group 15-49 years. It is estimated that India had approximately 1.2 lakh new HIV infections in 2009[9].

- Manipur, with 0.78% of the people having HIV, is the state having maximum number of HIV population, followed by Andhra Pradesh with 0.76% in the second place, Karnataka with 0.69% in the third place and Nagaland in the fourth place with 0.66%[8]

- No new HIV cases were reported from any states in 2010

- Most infections occur through heterosexual transmission. However, in certain regions use of injecting drug, men who have sex with men and single male migrants are contributing for the spread of HIV epidemic. HIV epidemic in India is found in certain groups. The HIV prevalence among the High Risk Groups, i.e., Female Sex Workers, Injecting Drug Users, Men who have Sex with Men and Transgenders is about 20 times higher than the general population.

- The mode of spread of HIV in the Southern part of the country is mostly through heterosexually. Whereas infections in the north-east are predominantly from illicit drug injection.

Trends of HIV in India, 2004-09

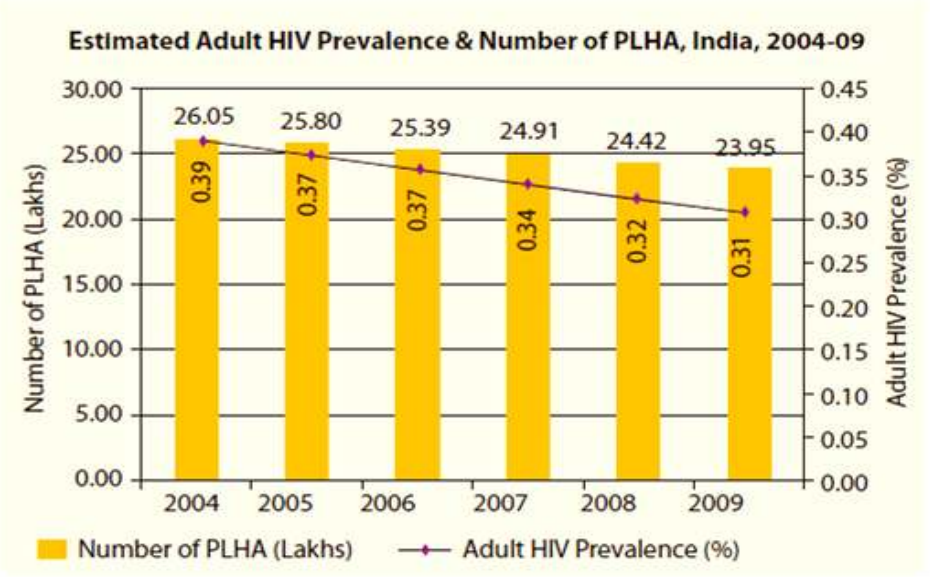


fig -1**Estimated Annual New HIV Infections in india**[10]

The scenario in Tamil Nadu[7]

Tamil Nadu, which had an alarmingly high incidence of HIV infection even 10 years ago, has dropped from third to fifth among states with the largest number of people infected with the deadly virus. The state previously ranked in the top three with 1.54 lakh HIV-positive people, it has now been overtaken by Karnataka (2.45 lakh), and West Bengal (1.67 lakh

HUMAN IMMUNODEFICIENCY VIRUS

Causative Agent:

- The causative agent of AIDS is Human immunodeficiency virus
- Family - human retroviruses (Retroviridae)
- Subfamily -lentivirus.
- Types ,
  - HIV-1
  - HIV-2.
- HIV-1-commonest all over the world and in India .
- Differences between the two are:

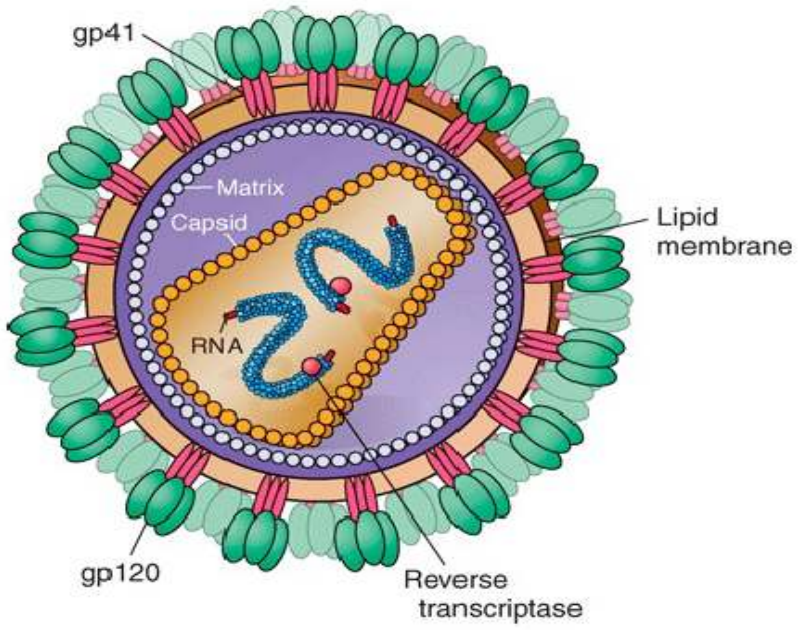
  1) The transmission efficiency of HIV-2 infection through sexual route is lower when compared to HIV-1.

  2) The incubation period of HIV-2 infection is reported to be longer than that of HIV-1.

Of the persons infected with HIV in India, 1.7%-4.6% due to HIV-2 alone, and 3.3%-20% due to combined HIV-1 and HIV-2.

Presence of dual infection of HIV-1 and HIV-2 and not of HIV-2 alone has also been reported among intravenous drug users from Manipur[8].

Fig-2 Structure of HIV Virus IV-



- Icosahedral structure, with a number of external spikes constituted by

2 major envelope proteins viz.

  - the envelope gp120
  - transmembrane gp41.

- After entry into cell infected cell's surface show budding virions and integrates various host proteins which includes major histocompatability complex (MHC) both classes antigens into lipid membrane
- There are three transcriptive units coding for the common viral structural proteins:

- The gag region for the viral core
- The pol region for the reverse transcriptase,
    - protease,
    - endonuclease
- The envregion for the 2 major envelop glycoproteins, mentioned above.
- gp120 situated on the external spikes of the virion,
- gp41 helps in the attachment of gp120 on the surface of the HIV.
- Apart from this structural proteins, other 4 virus encoded regulatory proteins have been recognized. They play a role in "checks and balances" controlling HIV replication. Viz:
- Two major genes tat and rev affect the events that enhance viral application, whereas
- The nef region down regulates virus replication.
- The vif region appears responsible for maturation of viral proteins at the time the virus bud from the cell.
- The early interaction of these regulatory proteins during acute infection of a cell by HIV determines the terminal outcome of this infection. For example, in the presence of high levels of nef gene expression, viral replication could be suppressed. Other viral genes, some specific for HIV-1 (vpu) or HIV-2 (vpr) have been identified,about their functions have not been fully identified.

Replication Cycle Of HIV[11]

1. Binding and entry

- HIV is a RNA virus, genomic RNA to DNA conversion occurs with the help of reverse transcriptase.
- gp120 protein binds to CD4 receptors on the host cell surface which marks onset of replication cycle.
- it fuses with one of the group of co-receptors
- Virus enters into specific cells.
- Other chemokine receptors involved are CCR5 receptors on monocytes and CXCR4 receptors on T cells. Strains of HIV utilizing CCR5 as a co-receptor are called as R5 viruses, and Those strains of HIV utilizing CXCR4 are called as X4 viruses.

Rarely individuals though had have sexual exposure to HIV in high-risk situations, remained uninfected. Retrospective Genetic analysis of these individuals showed an inherited homozygous defect in the gene that codes for CCR5. Population study showed that 1% of Caucasians of Western Europe in ancestry possessed the above homozygous defect. 20% had heterozygous defect. Homozygous defect in CXCR4 got the infection but manifested slow progression of the disease[1].

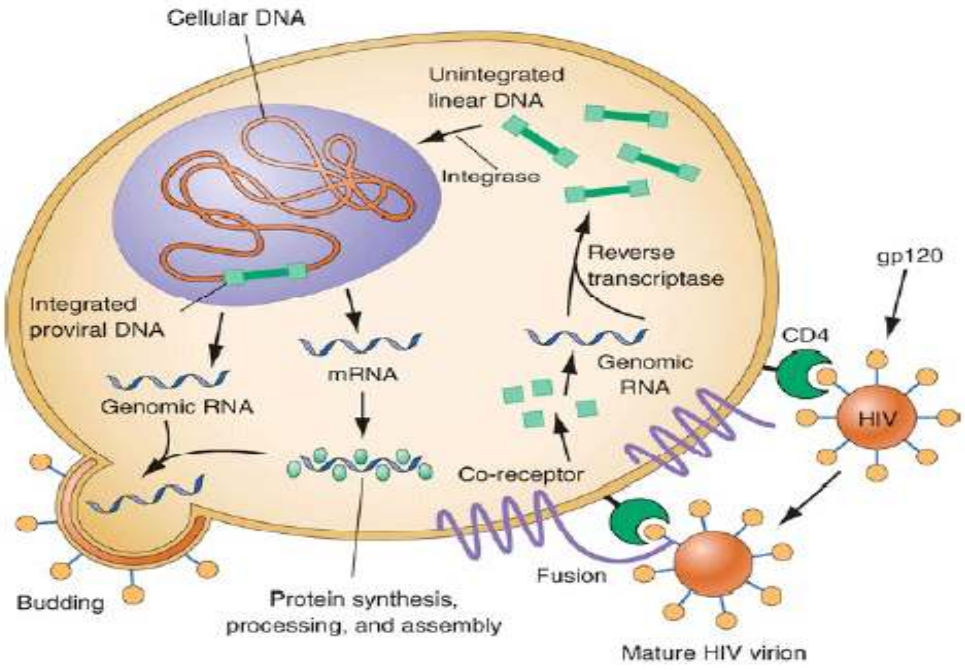
2. Reverse transcription, nuclear import, and integration of viral DNA

- Every virion has a store of reverse transcriptase enzyme,
- Catalyzes the reverse conversion of the genomic RNA into DNA.
- So formed DNA enters nucleus
- Integrase adds the formed DNA at random sites of the host cell chromosome through,.
- Provirus produced can be transcriptionally inactive (latent) or may actively produce virus.

3. Assembly of virus

- Soon after transcription, HIV m-RNA is converted into protein
- They undergo modification by glycosylation
- Then cleavage occurs.
- The virus constituted by proteins, enzymes, and RNA
- Stay at cell membrane of cells.
- Core acquires its envelop from the membrane.
- Protease enzyme mediates the conversion of gag-pol precursor to form the mature virus particle. [12]

Fig-3 **replication cycle of HIV** [1]



MODE OF TRANSMISSION[1]

HIV can be transmitted by

- Contacts homosexually and heterosexually
- through blood and its products; and by
- from infected mothers to infants either in intrapartum period, perinatal period or while breast feeding.

Sexual transmission

- Commonest transmission mode
- Developing countries, -heterosexually transmitted, but in many western countries male-to-male sexual transmission still occurs.

- Many factors influencing transmission

    a. viral load

    b. ulcerative genital diseases

- Such transmission inefficient.

- Per coital act risk was .12% /act when not on ART
- In developing country high rate in this analysis

- Female-to-male (0.38% per act and
- male-to-female transmission 0.30% per act,.
- HIV detected in semen both inside and outside infected cells .
- The virus accumulates in semen in inflammatory states such as urethritis and epididymitis, having numerous lymphocytes and monocytes in the fluid,
- Virus also isolated from cervical and vaginal secretions.
- High risk of HIV transmission with unprotected receptive anal intercourse (URAI) among both men and women when compared to the risk associated with receptive vaginal intercourse. Although data are limited, the per-act risk for HIV transmission via URAI was estimated to be 1.4% for both men and women in a recent systemic review/meta-analysis.

- Presence of other STDs increases the chance of spread of HIV because of ulceration of mucosa eg:
  - Treponema, pallidum,
  - H.ducreyi and
  - Herpes simplex.
- Studies done in Uganda showed that the main determinant of heterosexual transmission of HIV were :
  - amount of virus in blood.
  - If no circumcision done increased risk because more chance for micro trauma and increase in other STD.
  - Oral sex less efficient mode when compared to other modes
  - Alcohol abuse with illicit drug use along with unsafe sexual practices both homosexually and heterosexually doubles the risk.

Blood and its products

- HIV-screening done to blood and its products, or organ transplantation .
- sharing of used needles, syringes, the water used for mixing, or the cotton

- Parenteral transmission occurs with Intra Venous puncture; Subcutaneous or Intramuscular injections , even though these modes mistakenly interpreted as low-risk
- >90% of people get infected .
- Sources of blood transmitting HIV are:
    a. whole blood,
    b. packed RBCS
    c. , platelets,
    d. irradiated leukocytes, and
    e. plasma can
- Exceptions:
    1) hyperimmune gamma globulin,
    2) hepatitis B immune globulin,
    3) plasma-derived hepatitis B vaccine, and
    4) Rh_o immune globulin

While processing these products there will be inactivation or removal of the virus.

Occupational transmission of HIV

There is little, but definitive increased risk of HIV transmission in health care workers and laboratory workers. Following contact with infected materials chances of transmission are:

- Skin-0.34%
- mucous membrane - 0.09% if the injured and/or exposed person is not treated within 24 h with antiretroviral drugs.
- through intact skin has not documented
- Nonintact skin exposure reported, but the mean risk ; lesser than through mucous membrane exposure..
- from infected HIV health worker to patient is very rare, till now only four such cases has been reported worldwide.

Maternal to fetal / infant transmission

- Infected mother transmits the virus to her foetus during pregnant period or at time of delivery.
- Developing countries- commonest mode of transmission
- Vulnerable periods of transmission:
    I. first six months of pregnancy-28%
    II. delivery process-60%
    III. breast milk. -25%
- High chance of infection –earlier part of breast feeding
- Exclusive breast-feeding less chance of transmission than mixed feeding
- The first-born twin more chance of infection than second one
- Caesarean section lowers the risk.
- 18% -developed countries and from

- 28% - developing countries.
- Greater transmission in
    a) plasma viremia more in mothers,
    b) low maternal CD4+T Cells count and
    c) HIV P24 antibody levels,
    d) maternal vitamin A deficiency,
    e) prolonged interval between membrane rupture and delivery,
    f) chorioamnionit is during delivery,
    g) STDs ,
    h) preterm labour,
    i) Amniocentesis

The risk of transmission increases with level of HIV RNA in maternal blood, < 1000 copies / ml blood is associated with 0%, 16.6% among 1000 to 10,000 copies / ml. 22% (10,001 to 50,000 / ml), (50,000 to 1,00,000 / ml) and 41% >1,00,000 /. If mother suffers from acute primary infection during pregnancy, there is a higher rate of transmission to the fetus owing to the high levels of viremia. Zidovudine treatment of HIV infected mother (pregnant) from the start of the second trimester throughout delivery and for the baby for 6 weeks following birth decreases the risk from 25% to less than 5%.

Other body fluids

- HIV found in low titers in saliva but it would not transmit the disease .
- Innate antiviral factors in saliva; which are immunoglobulins like IgA , isotype
- Another mechanism sequesteration of virus by mucins along with thrombospondin 1 and aggregation and later cleared by host.
- No virus in tears, sweat, and urine[1.]

IMMUNO-PATHOGENESIS OF HIV/AIDS[12,14]

HIV infection is unique because host cannot eliminate the virus, so chronic infection; there is simultaneous progressing deterioration of immunity. Hence they become more and more immunocompromised thereby suffers from dangerous opportunistic infections as well as malignancies.[13]

Primary infection with the human immunodeficiency virus (HIV) composes of viremia with or without clinical symptoms to be followed by a long period of clinical latency. During this period, there is only little, detectable viremia, the number of infected cells in the blood are very low and it is extremely difficult to isolate virus from these cells. Pantaleo et al[12], have analyzed viral burden and levels of virus replication

simultaneously in the blood and lymphoid organs of the same individuals at various stages of HIV disease. They reported that in early stage of disease, there is a dichotomy between the levels of viral burden and virus replication in peripheral blood versus lymphoid organs. HIV disease is active in the lymphoid tissue throughout the period of clinical latency, even though only minimal viral activity is demonstrated in blood.[14,15]

HIV persists in the lymphatic tissue stimulates the immune system which strengthen virus replication and virus dissemination follows, clearance of newly produced HIV will not be possible[16].

Three dominant patterns of evolution of HIV infection are in vogue:[15,16]

l) Typical progressors

- Majority in this group
- Survival average 10 years[14].

II) Rapid progressors

- Only-10% are rapid progressors[14,16]
- Rapid course.

III) Long-term non progressors

- Only 5%
- No progression for long time.[14]

CD4 T cells count[17]

- main targets of HIV infection.
- a valid marker for the progression of the disease.
- decrease in CD4 count is due to:

  a) Direct virological mechanism that results from a HIV mediated cytopathic effect. (eg: direct killing of cells and syncytial formation).

  b) Non-virological mechanism (eg: autoimmune mechanisms, anergy, apoptosis, and virus-specific immune responses) triggered off during the course of HIV infection[17].

Stages Of Infection

- Entire sequence of events is approximately 7 to 10 years from seroconversion to death.
- The stages are.

  1) **Transmission of virus:** acquired through sexual contact, exposure to blood or its products, mother to child transmission.
  2) **Primary HIV infection** (Acute HIV infection or acute seroconversion syndrome). Incubation period average 2 to 4 weeks, maximum up to 6 weeks, characterized by mononucleosis or flu-like illnesses.

3) **Seroconversion:** takes place at 6 to 12 weeks following an established transmission event.

4) **Early asymptomatic phase:**, CD4+Tcell counts >500/_l

- the patient does not have any HIV related symptoms,
- persistent generalized lymphadenopathy involving 2 or more sites and skin manifestations such as seborrheic dermatitis present.
- Plasma viremia is generally low. The viral burden in the peripheral blood is extremely low and expression of HIV in these cells minimal.

5) **Early symptomatic HIV disease, (CD4+T cells 200 to 500/microltr):**

- The patients in this stage may have mild features of the disease
- Active replication of HIV virus in this period.

6) **Late symptomatic HIV disease- AIDS, (CD4+T cells 50-200/microltr):**

- Continuous replication of virus in the lymphoid tissue,
- Progressive destruction of this tissue (burnt out lymph node) and severe impairment of immune function.
- This stage is characterized by severe and persistent constitutional signs and symptoms of opportunistic

infections or neoplasms or both. Common examples are Kaposi sarcoma, PCP, toxoplasma gondii , widespread mycobacterium aviumintracellulare infections, candidiasis of oesophagus, lymphoma.

7) Advanced stage, (CD4 count < 50/microltr):

In this stage, patients may have AIDS defining opportunistic infections and malignancies. Certain opportunistic infections are more likely to occur with profound immune suppression such as CMV retinitis, cryptococcal meningitis, disseminated histoplasmosis, etc. Neurological disease is more prevalent at this stage of infection[1.]

DIAGNOSIS OF HIV INFECTION AND AIDS- INDIAN GUIDELINES

The moral issues vary from country to country; hence, it is imperative to know the national guidelines regarding HIV testing.

Objectives of HIV testing

1. Survey: the trend of HIV infection monitored in a population for intervening.

2. Safe Transfusion: blood, organs or tissues for donation.

3. Voluntary testing of HIV for the purpose of diagnosis

.4. To diagnose clinically suspected cases.

5. To evaluate and monitor cases of occupational exposure.

6. Research.

The laboratory tests for diagnosis of HIV constitute:

1. Indirect methods.

2. Direct methods.

1. Indirect methods

- **Screening tests.**
- **Supplemental tests.**

Screening Tests[19]

Simple/Rapid assays are based on the following

a. Agglutination assays

High sensitivity, low specificity, requires only few minutes to perform. also less expensive as it does not require equipment like ELISA reader.

b. DOT BLOT assays / COMB test

- The principle -immunochromatography.
- The assays are rapid, easy to perform,
- No need of complicated equipment.
- Positive- formation of color on a specific circle, dot or a line.

c. ELISA [20]

- Screening test.
- HIV-1 and HIV-2, detection.
- Sensitivity - 99.7% and the specificity ->98.5%.
- The first line test recommended by NACO (National AIDS Control Organization)

Supplemental tests

Being more specific than the screening tests, used to confirm screening tests are:

a). Western blot.

- Confirmatory test.
- Immunoblot test for various types of anti-HIV antibodies by blotting technique using a nitrocellulose membrane.
- Western blot test is only to be used in case of equivocal or discordant results of ELISA.,(national HIV testing)

b) Indirect immunofluorescence assay[20]**.**

- turns positive earlier in the course of the disease than conventional ELISA and Western-blot technique.

c) Radioimmunoprecipitation assay.

d) Rapid latex agglutination assay (modification of standard latex agglutination test).

2. Direct methods

Detection of viral genomic material.

- **(PCR):** for specific gene sequence in the middle of many.
  - **DNA-PCR** - early detection of HIV infection.

    It is a highly sensitive test, (detection of one infected cell per 1,00,000 cells) highly subject to the false positivity by means of contamination or by laboratory processing error.
  - **RT-PCR** - measures viral RNA.

  Both qualitative detection as well as quantification are presently available, Ultrasensitive RT-PCR assays have a detection limit of 50 copies per ml., Quantification or measurement of viral load is an essential parameter for initiation of antiretroviral therapy as well as for monitoring the therapeutic response.
- **NASBA (Nucleic Acid Sequence Based Amplification)**

  HIV-1 RNA may be quantified by RNA amplification using electrochemical luminescence.
- **b-DNA**- Branched DNA technology detects HIV RNA directly through amplification of signal from a captured viral genome.
- **P24 antigen capture assay.** There is brisk rise during initial weeks of infection.

- this test has greatest use as a screening test for HIV infection during acute HIV syndrome when P24 level is high before the development of antibodies.The disadvantage antigenemia is transient, limiting its detection.

➢ **Viral culture.**

- Expensive and labour intensive.
- Adherence to sterile technique is very crucial.
- Peripheral blood mononuclear cells are -cultured with uninfected donor cells with phytohemagglutinin for 3 days.
- Monitored every 3 days for 28 days or longer to assess:
    a. the formation of syncytia and
    b. Presence of HIV P24 antigen or RT in culture supernatants.

WHO/Govt. of India Strategies to detect HIV infections.

➢ Since there is a great risk for transmission of HIV through blood, screening of blood products is mandatory.

➢ Following strategies put forward by WHO for detecting HIV infection , they are:

Strategy I - ensuring donation safety. The serum is subjected once to ELISA; if negative, patient won't have HIV, if positive, blood not used, and the donor is not informed.

Strategy II - for surveillance and for the diagnosis only in the presence of some AIDS-indicator disease: if first ELISA is negative, the sample is considered negative. If positive, second ELISA done, utilizing a technique different. Result positive only if second ELISA is also positive.

Strategy III - for diagnosing asymptomatic individuals with high-risk behaviour, a third ELISA test reactive then HIV positive.

In resource-limited countries, the testing strategy can be followed which is less expensive and easy to perform. Under these circumstances, there is no need to confirm the ELISA/Rapid test/Simple test results by supplemental tests[18].

fig-4 Showing objectives of testing

Objective Of Testing	Prevalence Of Infection	Testing Strategy
Transfusion/donation safety	All prevalence	I
Surveillance	>10 % < 10 %	I II
Clinical sign / symptoms of HIV infection / AIDS	All prevalence	II
Asymptomatic HIV infection	>10 % < 10 %	II III

National Guidelines for Adults[21]

1) Symptomatic people: reactive with two different kits .

2) Asymptomatic people: three different kits reactive

3) Blood sample collected at a time is tested with the first kit. If reactive, then retested with the second then third kit.

The kits that are used in ICTC are: Trispottest, Trilenetest, Dot immunoassay .

CDC classification system

- The current CDC classification system is used for HIV-infected adolescents and adults
- Parameters are clinical conditions due to HIV infection and CD4+ T lymphocyte counts.
- Three ranges of CD4+ T lymphocyte counts and three clinical categories
- those with CD4+ T cell count of <200/L has AIDS by definition, irrespective of opportunistic diseases .
- Once in category B, it cant goback to category A, even if the condition resolves; it is applicable for category C[1]

Definitive AIDS diagnosis.(with or without lab diagnosis of HIV infection)[1]

- Candidiasis of the oesophagus, bronchi, trachea, or lungs
- Extrapulmonary Cryptococcosis,

- Cryptosporidiosis, diarrhea>1 month
- Cytomegalovirus disease of an organ other than liver, spleen, or lymphnodes
- Herpes simplex: mucocutaneous ulcer(s) (>1 month's duration); or bronchitis, pneumonitis, or esophagitis of any duration
- Kaposi's sarcoma <60 yrs
- Lymphoma, primary, of brain <60 yrs age
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, any site (pulmonarya or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jiroveci pneumonia
- Progressive multifocal leukoencephalopathy
- Toxoplasmosis brain

fig 5:Relationship of CD4 Count Development of Opportunistic Infection

CD4 COUNTPERmcL	DIESEASES
<200	MAC INFECTION HISTOPLASMOSIS CNS LYMPHOMA CMVRETINITIS
50-200	TOXOPLASMOSIS CRYPTOCOCCOSIS COCCIDIOMYCOSIS CRYPTOSPORIDIOSIS PNEUMOCYSTIS
>5OO	BACTERIAL INFECTIONS TUBERCULOSIS HERPES SIMPLEX HERPES ZOSTER VAGINALCANDIDIASIS HAIRY LEUKOPLAKIA KAPOSI SARCOMA

Drugs used in treating HIV[21]

Antiretroviral agents act at vary steps of the life cycle disturbing replication of virus. :

(i) *fusion inhibitors*-inhibits fusion of virus with cell

(ii) *reverse transcriptase inhibitors*-block enzyme reverse transcriptase

(iii) inhibit enzyme- integrase,

(iv) Blocking synthesis of viral protein

(v) Blocking protease enzyme-(*protease inhibitors*)

(vi) prevention of budding virions from getting detached from cell

Commonly used agents

1) reverse transcriptase inhibitors
2) protease inhibitors
3) fusion inhibitors
4) . New classes of drugs are under trial.

Fig 6 Classes of ARV drugs[21]

Nucleoside reverse transcriptase inhibitors (NRTI)	Non-nucleoside reverse transcriptase inhibitors (NNRTI)	Protease inhibitors (PI)
Zidovudine (AZT/ZDV)*	Nevirapine* (NVP)	Saquinavir* (SQV)
Stavudine (d4T)*	Efavirenz*(EFV)	Ritonavir* (RTV)
Lamivudine (3TC)*	Delavirdine (DLV)	Nelfinavir* (NFV)
Didanosine (ddI)*		Amprenavir (APV)
Zalcitabine (ddC)*	**Fusion inhibitors (FI)**	Indinavir* (INV)
Abacavir (ABC)*	Enfuviritide (T-20)	Lopinavir/Ritonavir (LPV)*
Emtricitabine (FTC)		Foseamprenavir (FPV)
(NtRTI)	**Integrase Inhibitors (new)**	Atazanavir (ATV)*
Tenofavir (TDF)*		Tipranavir (TPV)
	CCR5 Entry Inhibitor (new)	

MONITORING OF HIV INFECTION

Follow-up and monitoring is required for patients initiated on ART to watch clinical progress and monitoring wellbeing., CD4+ T lymphocyte counts is the best validated predictors of development of opportunistic infection among patients with HIV infection. Plasma viral levels also independently determine prognosis information with regard to AIDS, the risk of specific opportunistic infection has not yet been properly related to plasma viral levels. The current guidelines for initiating prophylaxis do not include criteria based on plasma viral levels.[21,22]

Fig 7 Monitoring toxicities for patients on ART[21]

	Day 0 (baseline) Before or at start of ART	At 15 days	At 1 month	At 2 months	At 3 months	Every 6 months	Consultation as needed (symptom-directed)
Clinical and adherence counselling	✓	✓	✓	✓	✓	✓	
Weight	✓	✓	✓	✓	✓	✓	
Hb	✓	✓ (if on AZT)	✓ (if on AZT)		✓	✓	✓
ALT *	✓	✓ (if on NVP)	✓ (if on NVP)		✓*	✓*	✓
Random blood sugar	✓					✓ (if on PI)	
CD4	✓					✓	✓
Urinalysis	✓					✓ (if on TDF)	
Lipid profile**	✓ (only planning for PI)					✓ (if on PI)	✓**
Pregnancy test for women with reproductive potential	✓ (if planning for EFV)						✓
HBV and HCV screening	✓ (if history of IDU, transfusion-related transmission)						

- LFT to be monitored every month for HIV patients coinfected with HCV.

- Fasting lipid profile done half yearly since PIs can cause lipid derangement. Especially In patients with history of coronary artery disease.

- Viral copies need not be routinely measured. it is only indicated when there is a disparity between clinical findings and CD4 count so that treatment failure can be assessed.

- Patients on ART should have TheirCD4 count for patients ART should be measured at 6 monthly interval

- Drug-induced hepatitis can be caused by nevirapine so LFT mandatory in 1st month

- With an AZT cause bone marrow suppression. So CBC to be done

- RBS estimated before and after starting ART since diabetes mellitus is a leading cause of morbidity. [21]

HIV and Neurologic Diseases[3,4]

Neurological disorders affecting HIV patients accounts for increased morbidity in a good number of patients with HIV infection. The neurologic disorders that develop may be either primary to the pathological processes of HIV virus or secondary to opportunistic infections or neoplasms. It can affect both central and peripheral nervous system.

Fig 8 Neurologic Diseases in HIV Infected people[1]

Opportunistic infections Toxoplasmosis Cryptococcosis Progressivemultifocal leukoencephalopathy Cytomegalovirus Syphilis *Mycobacterium tuberculosis* HTLV-I infection Amebiasis **Neoplasms** Primary CNS lymphoma	Myelopathy Vacuolar myelopathy Pure sensory ataxia Paresthesia/dysesthesia **Peripheral neuropathy** Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome) Chronic inflammatory demyelinating polyneuropathy (CIDP)

Kaposi's sarcoma **Result of HIV-1 infection** Aseptic meningitis HIV-associated neurocognitive disorders, including HIV encephalopathy/AIDS dementia complex	Mononeuritis multiplex Distal symmetric polyneuropathy **Myopathy**

NEUROPATHOGENESIS[13]

- HIV-infected individuals can develop various neurological abnormalities due either to opportunistic infections and neoplasm or to direct effects of HIV or its products.
- Referring to the latter aspect, virus isolated from brain tissue and CSF of these people with and without neuropsychiatry manifestations.
- The cell types which are mainly infected in vivo are monocytes migrated to brain from the blood as well as microglial cells originally residing there.

- HIV entry into brain is postulated to be partially, : virus infected cells are able to stimulate expression molecules for adhesion like E-selectins and (VCAM-1) on brain endothelial cells in brain vasculature.
- another mechanism: HIV gp120 increases the expression of (ICAM-1) in glial cells; by which HIV-infected cells enter inside CNS and resulting in syncytium complex. Virus isolates from the brain are preferentially R5 strains as opposed to X4 strains; with respect to this ,
- HIV-infected people having heterozygosity for CCR5D32 protectedfrom HIV encephalopathy compared to those who have homozygosity for the same.
- HIV-infected individual showed lesionsin white matter as well as neuronal loss in neuroimaging. Given the relative paucity of supporting evidence of HIV infection in neurons either in vivo or in vitro, it .Rather, the HIV-mediated effects on brain tissue are due to combination of neurotoxins secreted by monocytes and inhibition by gp120, reytes. In this regard, it has been demonstrated that both HIV-1 Nef and Tat can induce chemotaxis of leukocytes, including monocytes, into the CNS. Neurotoxins are usually released from monocytes as a result of infection and/or immune

activation. neurotoxic factors secreted by monocytes have been reported to kill neurons through (NMDA) receptor.

- In addition, HIV gp120 cause neurotoxicity by
    1) opposiing action of (VIP),
    2) raising intracellular calcium , and
    3) diminishing nerve growth factor level
- A variety of monocyte-derived cytokines can contribute both directly as well as indirectly ; these include TNF-α, IL-1, IL-6, TGF-β, IFN- γ, platelet-activating factor, and endothelin. In addition, infection and/or activation ofmonocyte-lineage cells can result in increase in eicosanoids, ,andquinolinic acid, which may contribute to neurotoxicity.
- It has been found out that HIV-infected individuals with the E4type allele inapolipoprotein E (apo E) have greater chance encephalopathy and neuropathy features
- The probability that virus and its products are responsible for neuropathogenesis is evidenced by the observation that neuropsychiatric abnormalities may undergo remarkable and rapid improvement upon the institution of ART, particularly in children affected with AIDS.[1]

CLINICAL FEATURES

- The nervous system - frequent and severe targets of (HIV) infection.
- 75% of all persons infected with HIV develop symptomswith respect to neurologic diseases. As stated above Neurologic disease in HIV infected population is not only common but also it is frequently both catastrophic and life-endangering.
- Neurological disease occurs with advanced immunosuppression and patient has other (AIDS)-defining illnesses,
- 15% of HIV seropositive persons it is the presenting feature of AIDS.
- Carefully scrutinizing CNS examination, even without the presence of definite problems pertaining to neurological involvement, frequently shows evidence central or peripheral nervous system involvement.
- Any portion of the neural network may be involved by a wide variety of neurologic diseases complicatingHIV-1. Illnesses affecting the nervous system due to HIV may be classified into primary illnesses directly due to virus and secondary illnesses, due to identifiable causes. Primary HIV-

associated disorders include brain-encephalopathy (dementia), spinal cord-myelopathy, peripheral nerve-distal sensory polyneuropathy (DISP), and muscle-myopathy. Secondary complications are mainly as the result of cell mediated immunity deficiency accompanying AIDS. The main infectious complications are

1) cerebral toxoplasmosis,
2) cryptococcal meningitis,
3) Cytomegalovirus (CMV) infection,
4) Progressive multifocal leukoencephalopathy

Other causes of neurologic disease include neoplasms both primary and metastsasis, drug toxicity, metabolic and nutritional diseases, and stroke.[23]

PRIMARY HIV-ASSOCIATED DISORDERS OF CNS[4]

HIV Encephalopathy / AIDS Dementia Complex

The term AIDS Dementia complex was introduced by navia and colleagues in 1986.HIV-associated dementia is the forerunner of AIDS-defining illness in a minority (3%) of patients with HIV infection and hence only rarely precedes clinical evidence of immunodeficiency. Clinically significant encephalopathy gradually develops in 25% of untreated patients with AIDS. As immunologic function declines, the risk

and gradation of HIV-associated dementia goes on rising. Autopsy series conducted suggests that 80–90% of patients with HIV infection have histologic evidence of CNS involvement[1].

Clinical Features

- most prevalent form of the neurologic complications of HIV –

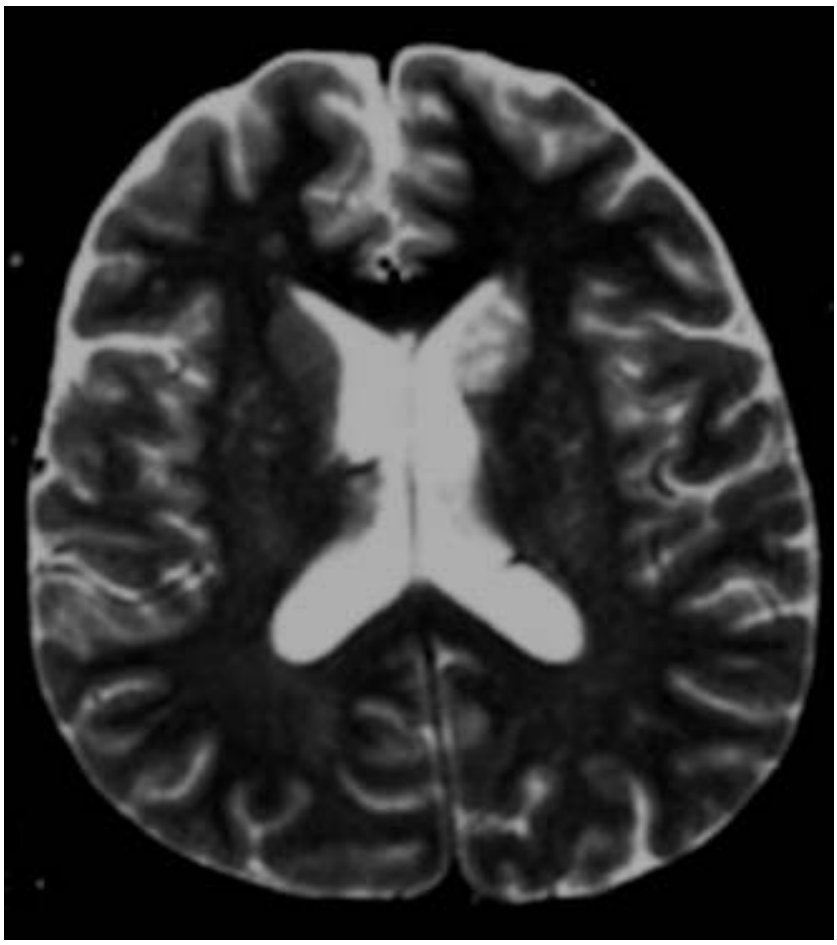


Fig 9-CT brain of HIV dementia-dilated ventricles, cerebral atrophy

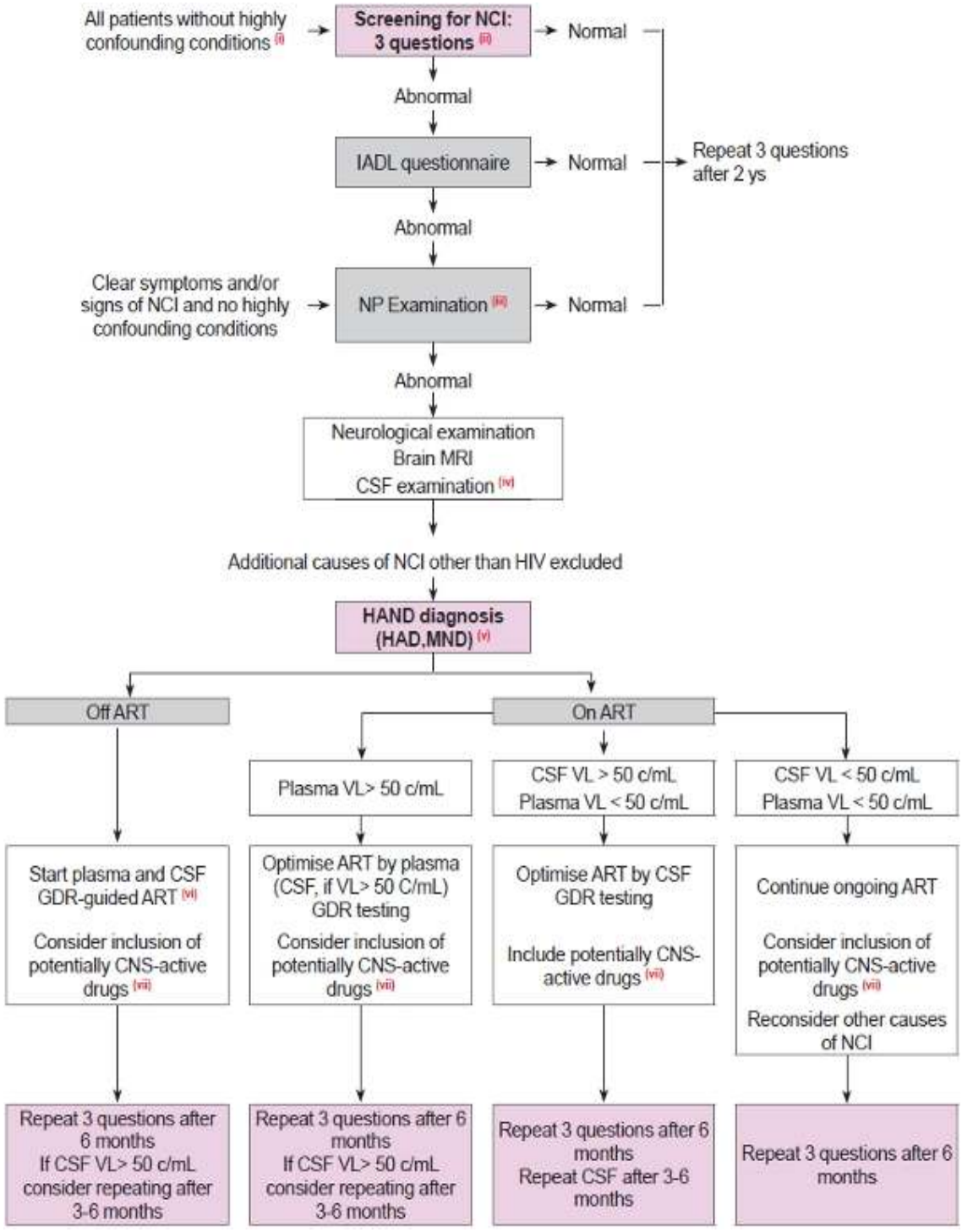


Fig 10-screening of HIV DEMENTIA

- Other terminologies (AIDS dementia complex: , HIV encephalopathy, multinucleate giant cell encephalitis, o: HIV-1-accompanied cognitive/motor complex).
- The symptoms of HIV dementia - three main categories:
  a) Cognitive, forgetfulness, sluggish activities, difficulty reading, concentration decrease.
  b) Motor, imbalance and limb weakness.
  c) Behavioural. – Lack of interest , social withdrawal, depression is a close differential diagnosis.
- Acute mania could be a first manifestation. Early , signs subtle to make a definite diagnosis.
- As dementia progresses, the more marked cognitive impairment develop psychomotor retardation as well as marked behavioural abnormalities can occur.
- At terminal stage, they develop paraparesis, incontinence,:tremor, or seizure,
- The onset and progression varies. Commonly, dementia occurs lately
- CD4 lymphocyte counts are usually below 200/mm.
- At times, first AIDS-defining illness
- Neurologic deficits progress either rapidly or slowly.

- How early neuropsychologic impairment occurs is controversial: whether subtle neurocognitive deficits precede the development of HIV dementia.

Diagnostic Studies

- To date no laboratory tests or neuroimaging study have been found to be specific for diagnosing HIV dementia,
- After excluding other causes we establish the diagnosis
- Blood VDRL and
- Cerebrospinal fluid for cryptococcal antigen).
- CSF abnormalities :
    a) elevated total protein,
    b) pleocytosis,
    c) globulin positive due to intrathecal synthesis
    d) oligoclonal bands.

(Similar CSF picture in neurologically asymptomatic patients with HIV infection.)

- Other dementia causes ruled out,
- Elevations of CSF B2-microglobulin, , and quinolinate, connected with the HIV dementia,
- Radiologic studies to rule out infections or neoplasms and supporting evidence of HIV dementia

- Neuroimaging shows
    a) Cerebral atrophy,
    b) Enlarged ventricles,
    c) White matter abnormalities.

All these are nonspecific, there seem to be importance for volume of the cerebrum that has undergone atrophy(more the atrophy on brain (MRI) more severe magnitude of dementia).

Pathogenesis

The clinical features show that there is predominant involvement of structures of subcortex , as evidenced by neuroimaging . The cause of cerebral atrophy is likely to be due to multiple factors, although there is an association between the ventricular expansions revealed by computed tomography (CT) scans. Microglial cells are increased in the cerebral cortex. Tyor and colleagues have proposed a unifying hypothesis for HIV dementia and several other neurologic disorders associated with HIV infection. They suggest that the abnormalities observed in HIV dementia, vacuolar myelopathy and sensory neuropathy are the consequence of infiltration of the CNS by macrophages and microglial with subsequent release of toxic cytokines, such as TNF and IL.

- Neuropathologic abnormalities depicted are
    a) inflammatory cell infiltration
    b) glial cell infiltration[21],
    c) widespread pallor in white matter .
    d) Pallor could be due to
        a) demyelination,
        b) alterations in BBB.
- HTLV) type III (HIV-l) is the cause of dementia, due to HIV gp41dendrites with their synapses are destroyed .Polymerase chain reaction magnifies HIV DNA.
- Connection between viral copies and encephalopathy found out
- Cells affected by HIV are:
    a. Monocyte/macrophage series
    b. Endothelial cells .
    c. Glial cells in pediatric AIDS encephalopathy.
    d. Astrocytes,
- Gpl20 cause death of neurons in vitro accompanied by the opening of calcium channels in cell membrane requires microglial cells. CCB- nimodipine prevent neuronal death
- Monocytes and astrocytes produce neurotoxic factors leading to glial proliferation.
- Cytokines, like TNF-α and IL-6, and arachidonic acid metabolites cause neurotoxic damage.

- Stimulation of N-methyl-D-aspartate (NMDA) receptors, just like other neurodegenerative disorders. Furthermore, Heyes and colleagues have demonstrated increased levels of the excito-toxin quinolinic acid; an NMDA agonist.

Fig 11 HIV Encephalopathy-stages[1]

Stage	**Definition**
0 (Normal)	Normal mental and motor function.
0.5 (Equivocal/subclinical)	Absent, minimal, or equivocal symptoms without impairment of work or capacity to perform activities of daily living. Mild signs (snout response, slowed ocular or extremity movements) may be present. Gait and strength are normal.
1 (Mild)	Able to perform all but the more demanding aspects of work or activities of daily living but with unequivocal evidence (signs or symptoms that may include performance on neuropsychological testing) of functional, intellectual, or motor impairment. Can walk without assistance.

2 (Moderate)	Able to perform basic activities of self-care but cannot work or maintain the more demanding aspects of daily life. Ambulatory, but may require a single prop.
3 (Severe)	Major intellectual incapacity (cannot follov news or personal events, cannot sustai complex conversation, considerable slowin of all output) or motor disability (canno walk unassisted, usually with slowing an clumsiness of arms as well).
4 (End-stage)	Nearly vegetative. Intellectual and social comprehension and output are at a rudimentary level. Nearly or absolutely mute. Paraparetic or paraplegic with urinary and fecal incontinence.

Treatment[3,4]

- HIV plays vital role, direct or indirect, in the pathogenesis of HIV dementia. Thus, soon after antiretroviral therapy became available, patients with HIV dementia was put on the same .

- Zidovu-dine (ZDV)used in adult HIV dementia and retarded the progression of encephalopathy in children. .
- Eearly treatment with ZDV is said to protect from cognitive impairment in AIDS.
- Dose of the prophylaxis: not yet determined
- AIDS patients receiving ZDV 1000 mg/day improved neuropsychologic performance compared to the patients. Hence higher doses used.
- If dementia progressing after administering high doses then stavudine [d4T] 40 to 80 mg/day may also be given in zidovudine intolerance.
- Although there are limited data to indicate the efficacy of this approach, improvement in neuropsychiatric test scores have been noted for both adult and paediatric patients treated with antiretrovirals. With initiation of Cart quick resolution of cognitive dysfunction shows that soluble mediators are involved in the pathogenesis and that problem is reversible. It is also worth mentioning that these patients have an increased sensitivity to the side effects of epileptic drugs. Using these drugs for symptomatic treatment is associated with an increased risk of extrapyramidal side effects. Therefore, patients with HIV encephalopathy who receive these agents must be monitored carefully. Several

experimental agents are under investigation in the treatment of HIV dementia, including nimodipine (calcium-channel blocker), memantine (NMDA antagonist), delavirdine and peptideT[22] .

Myelopathy

20% of patients with AIDS present with myelopathy, often as part of HIV-associated neurocognitive disorder

. Three main types of spinal cord disease are seen in patients with AIDS.

1. vacuolar myelopathy.

   Vacuolarmyelopathy characterized by usually a subacute onset and often presents with gait disturbances, mainly ataxia and spasticity;

   Which later may progress to include bladder and bowel incontinence.

   Physical findings include : increased deep tendon reflexes and extensor plantar responses.

2. The second form of spinal cord disease involves the dorsal columns presents as a pure sensory ataxia.

3. The third form is also sensory in nature

   presents with paresthesias and dysesthesias of the lower extremities.

   Autopsy showed Myelopathy in 38% of total cases .

Causes of myelopathy :

- toxoplasma,
- lymphomatous,
- granulomatous myelitis,
- necrotizing myelitis, due to varicella zoster
- Cytomagalovirus, and
- vitamin BJ2 deficiency.
- Diagnosis:
    a. MRI of brain with spinal cord screening
    b. CSF examination

(for ruling out infections and neoplasms.)

Pathology

- Direct: vacuolization in myelin , due to deposition of macrophages and glial cells.
- Indirect: through cytokines, particularly TNF.
- Although more important mechanism could be the metabolic deficits occurring more distal in the B12 utilization pathway .

Treatment

- There is no known treatment for AIDS-associated vacuolar myelopathy.
- Antiretroviral agents do not appear to offer benefit, although controlled trials have not been done.

- The methionine, a critical substrate in the B12 metabolic pathway, is under trial in the management of AIDS myelopathy.
- Specific therapy :

  antispasticity agents (i.e. baclofen),

  treatment of sphincter disturbance

  physiotherapy.[22]

Peripheral Neuropathy

Distal Symmetric Polyneuropathy

- most common form .
- rarely early in the course of HIV disease,
- risk increases with declining CD4 cell counts. .
- clinical or electrophysiological anomaly only 35% ; but
- pathologic evidence of DSP 90% [27]
- The presenting features in DSP :
  - numbness
  - burning sensation and
  - foot paresthesias
  - severe that patients experience pain on contact and walking difficulty
  - later distal muscle weakness developes

- CNS examination : pain and thermal loss in palms and soles , absent proprioception, and sluggish ankle reflexes increased knee reflexes.
- The mechanism - unknown.

Pathology:

- dying back neuropathy
- affects all types of fiber,
- peripheral nerve infiltration with predominent macrophage along with TNF-α, IL-1, and other
- many other cytokines involved.

Conditions causing DSP, :

- vitamin deficiencies (B6, vitamin B12)
- diabetes
- alcohol abuse.
- Drugs like vincristine and antiretroviral nudeoside analogues didanosine (ddl), zaldtabine (ddC), and stavudine (d4T) .
- those past history of neuropathy subclinically more susceptible.
- cumbersome to differentiate between drug induced neuropathy and HIV induced. Numb feeling, tingling sensation, lancinating pain common to both
- distal extremities mainly affected, severety more in the lower limbs, upper extremities spared till late .

- DSP may evolve slowly, whereas drug induced neuropathic symptoms progress more rapidly.
- Improvement of symptoms after drug cessation**.**

Treatment

- Reduce doses of ART
- analgesics, tricyclic antidepressants- Amitriptyline, antiepileptics[22]
- acupuncture under trial.

INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Inflammatory demyelinating polyneuropathy (IDP) presents as

- Ascending type of weakness,
- Absent reflexes
- Less of sensory disturbance
- Like GBS or CIDP as seen in seronegative patients.
- Develop in early part of HIV
- some present at the time of seroconversion .

IDP occuring late CMV should be thought of as a cause.

Diagnosis:

CSF:

pleocytosis in HIV-infected patients with IDP, whereas HIV-negative patients tend to have albuminocytological dissociation in cerebrospinal fluid**.**

Treatment

Since IDP is most likely mediated by autoimmune mechanisms and has responded, in many uncontrolled series, to immunomodulaters, including corticosteroids, plasmapheresis, and intravenous immunoglobulin.

Progressive Polyradiculopathy (PP)

The presenting symptoms : are

- Paraesthesia in leg and sacral area,
- flaccid weakness of lower limb,
- absent reflexes,
- Loss of sensation,
- Retention of urine**.**

Diagnosis :

- CSF shows pleocytosis, - lot of neutrophils
- cerebrospinal fluid culture is positive 50%
- primarily due to CMV infection of nerve roots**.**

Treatment:

- before irreversible necrosis of the nerve root sets in treatment instituted
- improvement in neurological status or stabilization with gancicyclovir. Other causes of progressive polyradiculopathy in AIDS :
  - syphilis,
  - lymphoma, in leptomeninges
  - tuberculosis.[22]

Mononeuritis Multiplexa

- multifocal, asymmetric, lesions involving both
- cranial nerves-facial or vocal cord palsy
- peripheral nerve lesions, as for example, -wrist drop or foot drop,
- tingling symptoms.
- initial stages of HIV infection, disease process confined to one or few nerves
- subsides on its own without any treatment.
- as HIV disease advances, CD4 counts goes below 50 cells/cumm, progress quickly to quadriparesis.
- misdiagnosed as IDP, DSP, .

- extensive form of mononeuropathy multiplex due to CMV virus and gancyclovir therapy[22] produces some improvement.

Myopathy

Clinical Features

HIV-associated myopathy develope irrespective of CD4 count.

- Proximal muscle weakness, -cannot get up from chair or climb stairs.
- Myalgia a nonspecific symptom in HIV infection.
- Loss of weight
- can be a reason for HIV wasting syndrome.

Diagnosis:

- Creatine kinase (CK) - most sensitive serologic test CK is increased in myopathy, average of 500 U/L. not by itself diagnostic of myopathy. The presence of proximal muscle weakness,along with supporting electrophysiological, is necessary for the specific diagnosis of myopathy,
- Electromyography (EMG) - useful in doubtful cases.
- muscle biopsy in HIV-associated myopathy can also be considered which display less interstitial inflammation than that present in HIV-negative polymyositis. Other findings in HIV myopathy are

A. inclusions,

B. nemaline bodies,

C. cytoplasmic granules,

D. mitochondrial anomalities[23].

Pathogenesis

- The pathogenesis - unknown, although
- immune mechanisms same as HIV-negative polymyositis.
- infect monocyte/macrophage lineage cells, myofiber infection has not been detected.
- other opportunistic infections causing myopathy :

- parasite-Toxoplasmosis
- virus-CMV,
- fungus-Microsporida, Cryptococcus neoformans,
- Bacteria-Mycobacteriumavium-intracellulare and Staphylococcus aureus.
- Drug induced myopathy -ZDV. ZDV toxicity level contributing to underlying myopathy not known
- And whether there are distinguishing features controversial. Morgello and associates[39] reported a quantitative morphologic study in which the degree of mitochondrial abnormalities was similar in patients treated or untreated with ZDV and was with

regard to the extent of myofiber degeneration. Red ragged fibers are a histologic hallmark of zidovudine-induced myopathy.(HH)

MR spectroscopy, cytochrome C oxidase deficiency, mitochondrial DNA abnormalities, have shown evidence for drug induced myopathy and animal models.

Treatment

- Patients with severe limb weakness should be subjected to withdraw the drug or reduce the dose. ZDV-treated patients that showed subjective improvement in muscle strength after ZDV discontinuation varies among between 18% to 100%. , a minority improves with ZDV withdrawal, .
- Prednisone therapy can be used,
- . Patients with or without inflammatory infiltrates responds to steroid
- oxandrolone, an anabolic steroid, resulted in weight gain, but not objective strength improvement, in patients with HIV myopathy and wasting syndrome

SECONDARY HIV-ASSOCIATED DISORDERS OF NERVOUS SYSTEM

Mycobacterium Tuberculosis

- Tuberculosis is the most commonest HIV related opportunistic infection in India contrary to p.carini in western countries. A study from Western India showed 57 out of 64 HIV seropositive cases as having tuberculosis
- Immunosupressed individuals and immunocompetant have difference in clinical presentation
- diffuse infiltrates in lung or mediastinal lymphadenopathy, more of extrapulmonary involvement .

HIV infected individuals can develop any form of tuberculosis, especially developing extrapulmonary tuberculosis ,example tuberculous meningitis more chance. HIV infection progresses more in patients hastenly with tuberculosis. the risk of developing active tuberculosis increased by a factor of 15 to 30.Unusual predilection in the form of lower lobe involvement, extrapulmonary affection, diarrhea, and meningitis are common in HIV patients.

- 669% chance tuberculosis in AIDS cases in a recent study, where 54.5% atypical. Progression of disease result in CD4 lymphocytes decline in quantity and quality; hence immune

system can't arrest the multiplication and spread of mycobacterium tuberculosis.

- Commonest form of extrapulmonary disease is:
    I. lymphadenopathy
    II. pleural effusion, Serous effusions are more common
    III. pericarditis
    IV. miliary disease,
    V. bone involvement
    VI. meningitis.

CNS involvement: M. Tuberculosis can cause

- meningitis,
- tuberculoma,
- brain abscess,
- myelopathy, or
- radiculopathy.

It can occur at any stage of HIV infection, and is often intracerebral and accompanied by anergy to skin testing. central nervous system involvement in patients with tuberculosis was five times higher in seropositive than in seronegative patients. Patients present with insidious onset of headache, fever and malaise, followed by meningismus, cranial nerve deficits, seizures and

altered mental status. meningeal signs were absent in one third of these patients, and altered mentation was present in less than half.

- HIV-infected patients with tuberculosis more chance for meningeal involvement, no change in clinical manifestations or the course of TB meningitis.
- prognostic factors in TB meningitis
    I. clinical stage at presentation.
    II. duration of illness,
    III. miliary disease,
    IV. Using alcohol ,
    V. age,
    VI. racity,
    VII. basilar meningitis
    VIII. vascular compromise
    IX. low CD4 count.

- No alteration in presenting features except for
    I. Severe cognitive dysfunction in HIV-affected patients.
    II. basal meningeal enhancement and hydrocephalus not commonly seen

III. fewer basal exudates and numerous tb bacilli in cerebral cortex and layers of meninges .

IV. lower leukocyte counts in blood and CSF fluid

- When M.tuberculosis affects the intracranial arteries stroke results , anterior circulation is the most common site.
- A patient with AIDS who have a focal CNS lesion without focal neurological signs are more likely to have Toxoplasmosis than Tubeculosis. In patients with Mycobacterium avium intracellulare, single or multiple mass lesions are more common than meningitis. Computed tomographic characteristics are diverse and include ring-enhancing lesions , infarcts. rarely, the CSF normal. Negative microbiologic studies of the CSF are not unusual, resulting in treatment for presumptive infection. Meningeal or brain biopsy may be required to firmly establish the diagnosis. The response of AIDS patients to the standard therapy M tuberculosis is generally gratifying

Fig 12-tuberculoma

Toxoplasmosis

- Manifest as cerebral mass lesion .
- incidence of 3% to 40%.
- the reactivation of old acquired endogenous infection showing lack of IgM antibodies in patients.
- multicentric lesions and choroid plexus lesion -hematogenous spread of parasites from systemic organs
- developes when CD4 counts goes below 200cells/cumm,
- the AIDS index- Central nervous system toxoplasmosis usually results and it is the diagnosis in half of the cases.

Clinical Features

- Toxoplasma encephalitis[47,48] present with either focal or generalized.
- headache (55%),

- confused state (52%),
- fever (47%),
- tiredness(43%), and
- convulsions29%).
- Focal neurological deficits;,
    I. hemiparesis,
    II. falling while walking, and
    III. palsy of cranial nerve.
- encephalopathy usually develop focal neurological deficit with evolving diesease
- subacutely progression**.**

Diagnosis:

- CT brain- show single or multiple ring enhancing lesions.
- a higher number of lesions is shown in MRI studies and, in some cases, show abnormalities unrecognized by CTscans.
- Serum anti-Toxoplasma antibodies are measured,but low or absent titer does not rule out the diagnosis.
- in patients with antibodies to the organism more chance for having cerebral toxoplasmosis than who are negative for the antibodies .sensitivity more with Immunofluorescence assay than enzyme-linked immunosorbent assay for detecting antibody.

- Polymerase chain reaction of the cerebrospinal fluid may be a promising tool in the diagnosis of cerebral toxoplasmosis.
- thallium single-photon emission computed tomography or 18F-fluorodeoxyglucose positron-emission tomography can be done to rule out central nervous system lymphoma.

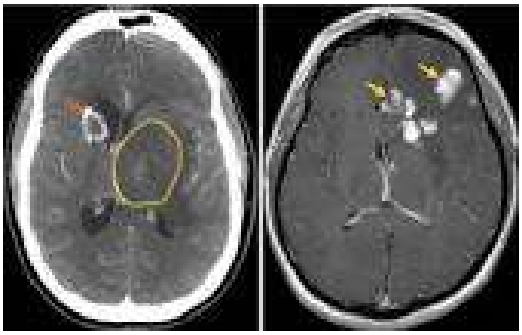


Fig 13-toxoplasmosis in brain

Treatment

- with large mass lesions producing midline shift with herniation, decompression can be done. ,
- empiric therapy started for those people with CT/MRI findings consistent with toxoplasma and rising titre of antibodies to the organism .
- oral pyrimethamine and sulfadiazine . Standard treatment with above regimen with leucovorin(5 to 10 mg/day) is required for atleast minimum of 4 weeks since former produce bone marrow depression. Adverse effects of

sulfadiazine, are rash and nephrotoxicity, seen in 44% of patients.

- Clindamycin(2.4 g/day) and pyrimethamine 75 mg/day can also be used for Toxoplasma encephalitis. 83% showing improvement of symptoms in seven days of regimen.
- stereotactic brain biopsy done, if no clinical or radiological improvement in 2 weeks of empiric therapy for, other diagnosis should be sought **.**

Prophylaxis:

- primary prophylaxis: CD4+ T cell counts <100/L and IgG antibody present
- Secondary prophylaxis/maintenance therapy for people with history of prior toxoplasmic encephalitis since Relapses can occur, -sulfadiazine, pyrimethamine, and leucovorin when their CD4+ T cell counts go <200 cells/L. and it can be stopped when CD4+ T cell counts is maintained to >200/L for 6 months.
- the same everyday dose of -a double-strength tablet septran given for *P. jiroveci* prophylaxis ,gives protection for toxoplasmosis as well..[1,22,48]

Cryptococcal Meningitis

- Cryptococcal meningitis is the meningitis caused by fungus
- very common in HIV-infected patients in .in India.
- Generally occurs in more than 5% of patients with advanced disease in whom CD4+ T cell counts are below 100/microltr. The causative organism, Cryptococcus neoformans, may induce only little inflammation in AIDS patients with decreased immunity
- There is paucity of neck stiffness and photophobia, which favour meningeal involvement.

Clinical features:

- fatiguebilty, gastrointestinal disturbance,
- headache in majority.
- Cranial nerve palsies
- psychiatric disorders,
- Aphasia
- seizures .

Diagnosis:(CSF is the specimen used for all the tests mentioned below)

- India ink stain is used to establish diagnosis of Cryptococcal meningitis :CSF is the specimen,
- Titre of Cryptococcal antigen - 1:8
- cerebrospinal fluid culture.

Treatment:

- Intracranial hypertension managed by lumbar punctures, VPshunt and acetazolamide
- acute infection: IV amphotericin B, or liposomal formulation of amphotericin, with flucytosine 25 mg/kg qid for at least 2 weeks and, if possible, until the CSF culture turns negative. fluconazole 400 mg/d PO *8 weeks, and then fluconazole 200 mg/d until the CD4+ T cell count has increased to >200 cells/L * 6 months.
- fluconazole and itraconazole advantage
    a. Less adverse effects so can be used for longer duration to prevent relapse.

Adverse effect:

I. Amphotericin B - fever and glomerulonephritis rarely leukoencephalopathy. A liposomal form of amphotericin B doesn't produce above side effects.
II. Flucytosine bone marrow depression and gastrointestinal disorders.

Primary Central Nervous System Lymphoma

- Earlier days rare occurence, but now incidence has risen over past one decade
- . more prone to develop in those with CD4 counts < 100/cumm.

Diagnosis: Epstein-Barr virus in AIDS related PCNSL tissue as well as CSF, detected by polymerase chain reaction.

Clinical features:

- confusion, lethargy, and memory loss,
- often associated with headache and focal neurological signs**.**

Diagnosis:

- CT/MRI reveal single or multiple homogeneously ring enhancing lesions. Close differental diagnosis is toxoplasmosis , single lesion on MR imaging, with no antibody against toxoplasma establishes lymphoma
- stereotactic biopsy for Definitive diagnosis

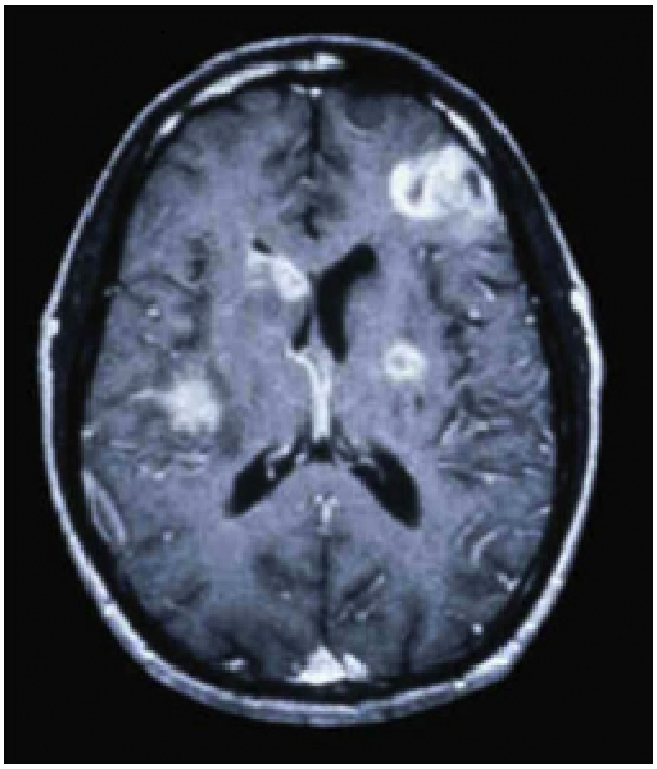


Fig 14 primary cns lymphoma

Prognosis: PCNSL in AIDS bad prognosis wont survive more than a month in the case of untreated cases. Radiation therapy may improves neurological status as well as life's qualityPatient can live upto 4 to 8 months with therapy

Treatment

Radiation therapy combined with chemotherapy is currently being evaluated in prospective clinical trials.

Non-Hodgkin's Lymphoma

The AIDS-associated lymphoma's neurological complication is metastases to the central nervous system by non-Hodgkin's lymphoma, which are typically meningeal rather than intraparenchymal. Neurological

disease may either herald the tumor, or the latter may remain occult despite repeated lumbar punctures.

Clinical feature: Affected individuals may present with

- altered cognitive function,
- cranial neuropathies,
- or spinal root lesions,
- meningeal lymphomatosis and carcinomatosis seen in the absence of HIV infection**.**

Diagnosis: In addition to repeated

- cerebrospinal fluid analyses,
- bone marrow biopsy and
- abdominal CT.[22]

Progressive Multifocal Leukoencephalopathy

- causative agent-JC virus,a human polyyoomavirus.
- HIV infection is the most common immunodeficient state predisposing to PML, In a review of 150 cases of PML from south Florida seen between 1981 and 1994, two occurred with diseases other than HIV infection. Four percent of patients with AIDS develop PML during the course of illness, but 29% of these cases represented the initial manifestation of AIDS.

Clinical features:

- altered sensorium,
- speech and decreased vision,
- difficulty walking,
- Weakness of limbs

Diagnosis:

- CT scans typically show hypodense, non enhancing lesions, most common location parietal and-occipital lobe without oedema.
- MRI- investigation of choice in PML lesions ,T2- weighted spin-echo.
- PCR for JC virus DNA .

Prognosis:

- average survival : 2 - 4 months.
- 8% benign course, can have any of the three ,remission, survival, or spontaneous recovery.
- Good prognosis:

    a.higher CD4 counts (>200 cells/mm3),

    b. CT-contrast enhancement

    c. HPE-inflammatory infiltrates .

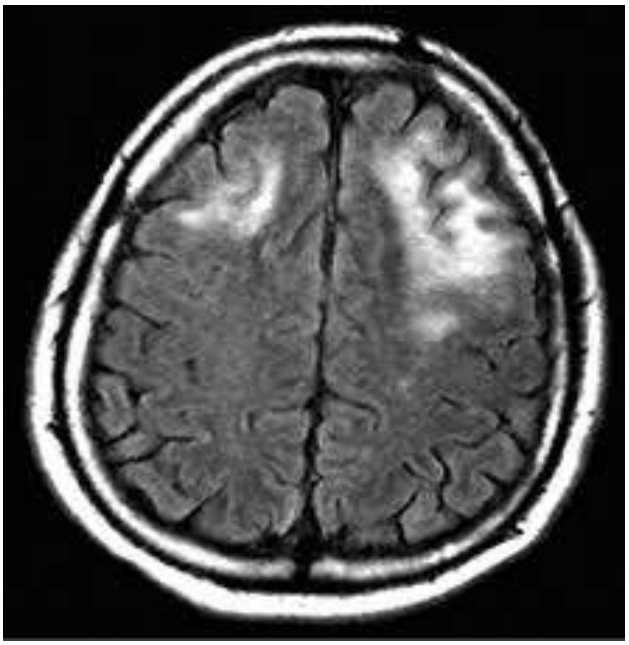


Fig 15- **Progressive Multifocal Leukoencephalopathy**

Treatment:

- no specific treatment
- average survival - 2 years and
- seldom survival >15 years with PML on cART
- . Despite having a significant impact on survival, only 50% of patients with HIV infection and PML show neurologic improvement with cART. Studies with other antiviral agents such as cidofovir have failed to show clear benefit.
- favorable prognosis for PML in HIV infection include a
    I. CD4+ T cell count >100/L
    II. HIV viral load of <500 copies per milliliter.[1]

- There is only limited information about treatment
- Intravenous cytarabine (Ara-C) tried. .in a analysis of the first 60 patients enrolled in this trial failed to show efficiency of Ara-C in the treatment of AIDS-associated PML Several chemotherapeutic agents have been documented to have in vitro antiviral activity against the JC virus, including camptothecin and topotecan; however, both are toxic and await evaluation in clinical trials.
- despite widespread use of Cart PML still possible [1]

Cytomegalovirus:

CMV can result in a constellation of central As well as peripheral nervous system disorders in AIDS, :

- CMV encephalitis,- a cause of dementia in AIDS patients
- Seen in patients with CD4 count < 50 cells/cumm
- common pathologic finding in brain - microglial nodule , rarely
  - CMV inclusions.
- Common targets- brain stem and spinal cord .
- Adrenal glands are also affected.
- associating other infections

a) toxoplasmosis

b) zoster

c) Cryptococcus

d) PML

- myelitis,
- polyradiculopathy, and
- mononeuropathy multiplex..

Clinical Features

- close differential diagnosis : HIV dementia.
- Sudden altered sensorium
- more brain stem involvement

Diagnosis:

- CT scan: hydrocephalus ,periventricular or meningeal enhancement.
- retinal fundi :any CMV retinitis.
- Electrolyte abnormalities due to adrenal failure
- specific serologic or laboratory tests not available for confirmation of CMV encephalitis
- reliable investigation: polymerase chain reaction for CMV DNA

Treatment

- average survival time for CMV encephalitis -5 weeks,
- antiviral therapy no role
- drugs: ganciclovir or foscarnet.
- Only 38% Ganciclovir penetrates blood-brain barrier

- Alternate drug: foscarnet
- A current research is evaluating the utility of polymerase chain reaction measures of CMV DNA in the cerebrospinal fluid and the efficacy of antiviral agents in the therapy of these disorders.

Syphilis

- Is also a differential diagnosis of neurological disease in HIV-patients
- Overlap of neurological diseases in retrovirus and spirochaetes

Clinical features:

- acute meningitis,
- neuropathies of cranial and peripheral nerves,
- memory problem;
- stroke, and
- spinal cord diesease.

Diagnosis:

- :both produce alike CSF picture,- persistent pleocytosis.
- Although cerebrospinal fluid VDRL positivity is diagnostic of syphilis, sensitivity - 30% to 70%. In those with symptoms suggestive neurosyphilis having positivity of serum VDRL, negative cerebrospinal fluid VDRL, intravenous high-dose penicillin can be instituted . with a negative cerebrospinal fluid VDRL treatment given

a. protein exceeds 65 mg/dl
b. cerebrospinal fluid pleocytosis is greater than 20 cells/cumm.[23]
c. HIV infection alone cannot produce this picture

- Elevated cerebrospinal fluid IgG or cerebrospinal fluid oligoclonal bands on electrophoresis are present in both HIV infection and neurosyphilis and therefore are not likely to be diagnostically helpful.

Treatment:

- Those having HIV infection no adequate response to usual treatment rather, accelerated progression of neurosyphilis.
- aggressively treat syphilis in the HIV-affected patient.
- aqueous penicillin G (12 to 24 million units/day) ten days-treatment of choice
- response to therapy assessed by Serum and cerebrospinal fluid testing .
- Follow up-2 years
- aim- CSF values , VDRL titers should normalize
- cerebrospinal fluid abnormalities may persist due to simultaneous HIV infection.retreatment if the cerebrospinal fluid profile does not improve or deteriorates or if clinical symptoms suggestive of neurosyphilis development.

MATERIALS AND METHODS

STUDY AREA

General ward, ICU, General Medicine OPD, ART Centre and Neurology OPD of Government Coimbatore Medical College Hospital (CMCH), Coimbatore, a tertiary care centre in south India.

STUDY POPULATION

The subjects of the study will be all adult HIV patients admitted to Medical Units with Neurological manifestations during the study period and alsoHIV Patients Reviewed at the ART Centre and Neurology OPD at CMCH with Neurological manifestations developed after the diagnosis of HIV, presenting to the clinic during the study period who fulfil the inclusion criteria.

Inclusion Criteria:

1. All adult HIV patients with neurological manifestations presenting to CMCH, Coimbatore who are willing to take part in the study.

2. The subjects must have been an already diagnosed case of HIV, before developing the neurological manifestation.

Exclusion Criteria:

1. Patients not willing to take part in the study

2. Patients with pre-existing neurological disease, psychiatric patients, children and pregnant women.

3. Newly detected cases of HIV, where the neurological complaints were the presenting features or suffering from the neurological manifestations before the diagnosis of HIV.

4. Patients with other Neurological problems unrelated to HIV (neuro-degenerative diseases, neuro dystrophies)

5. Patients with co-existent Hep B and Hep C infections.

SAMPLE SIZE:

The sample size for the study is obtained using the equation:

$$n = \frac{\left({}^{Z}\frac{1-\alpha}{2} + {}^{Z}(1-\beta) \right)^2 \, x\sigma^2}{\delta^2}$$

where

${}^{Z}\frac{1-\alpha}{2}$ → 1.96 at 5% level of significance

${}^{Z}(1-\beta)$ → 0.482 at 80% power

σ → Assumed standard deviation

δ → Desired precision

$$= \frac{(1.96 + 0.842)^2 \times (2.1)^2}{(0.7)^2} = 71 \text{ samples}$$

STUDY DESIGN:

A cross-sectional study.

STUDY INTERVENTION:

Our study will be conducted in the General ward, ICU, General Medicine OPD, ART Centre and Neurology OPD of Government Coimbatore Medical College Hospital (CMCH), Coimbatore. Over the study period of 12 months, all adult patients, who fulfils the inclusion criteria will be enrolled in the study. The diagnosis of HIV will be defined as per the National Aids Control Organisations criteria.

Along with initial routine assessment, written informed consent will be obtained from eligible patients/ their relatives. They will undergo the treatment according to their clinical status.

The patients are free to discontinue from the study at any point of time according to their will and there will be no change in the treatment instituted to them irrespective of their willingness to continue/discontinue from the study.

STUDY DURATION:-

1 year

DATA COLLECTION FORM

(Enclosed in Annexure I)

STATISTICAL METHODS

The statistical analysis will be carried out using the software SPSS version 22.0. All the data will be expressed as Mean ± Standard deviation. Comparison of the means will be done using the unpaired T test or Mann Whitney U test. One way ANOVA will be applied to compare the different means. A p-value <0.05 will be considered as significant.

DATA COLLECTION TECHNIQUE AND TOOLS

The data was collected from the eligible subjects in the data collection form after obtaining the informed consent. The data was then entered in Microsoft Excel sheet. For statistical purposes, the data was transferred to SPSS software and the analysis and charts were prepared.

OBSERVATION & RESULTS

Sex Ratio

The sex ratio of the subjects in the present study is 1:2.2

TABLE 1: SEXRATIO

Male	Female
51	23

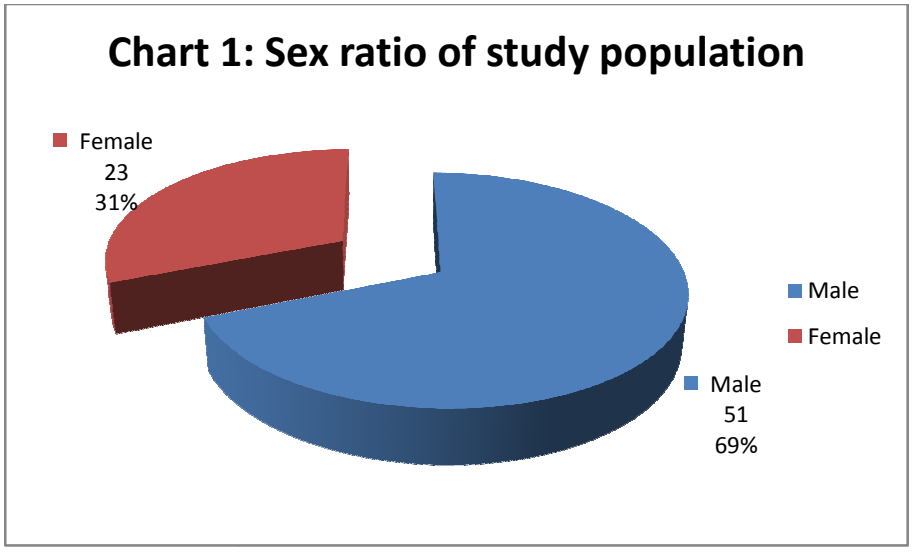


Table 2- Average age of the study subjects

Sex	Average Age
Male	33.27451
Female	33.43243
Combined	33.69565

Table : 3 Age & sex wise distribution of study subjects

Age group	Total	Males	Females
18-25	9	5	4
25-35	40	29	11
35-45	23	16	7
45-55	23	1	1

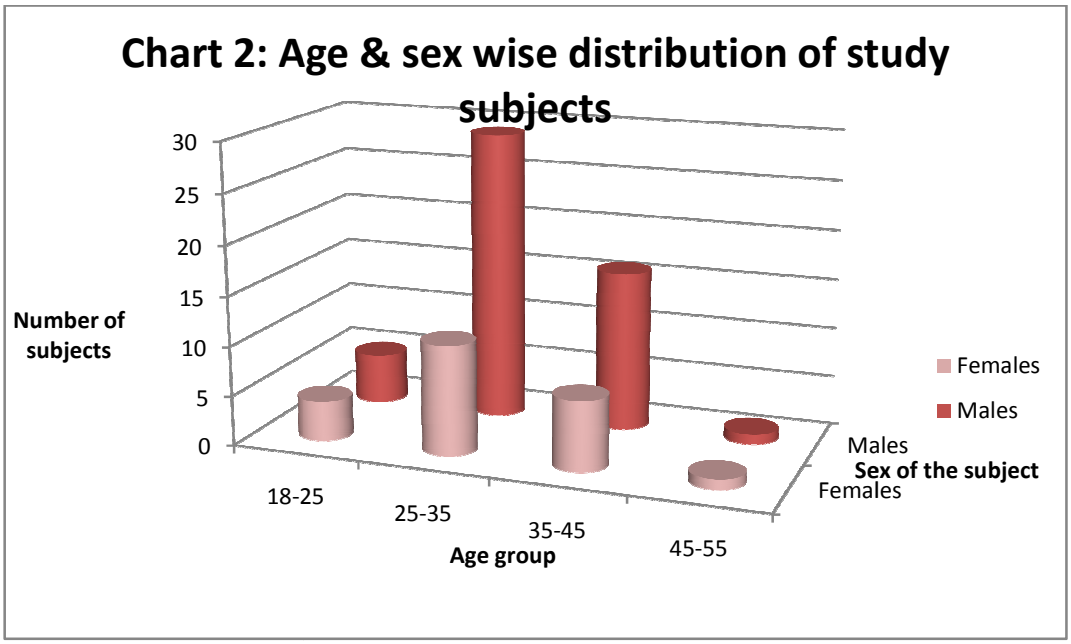


Table : 4 Nativity of the study subjects

Nativity	Number of subjects
Coimbatore	54
TamilNadu but outside Coimbatore	12
South INdia other thaN TamilNadu	5
North INdia	3

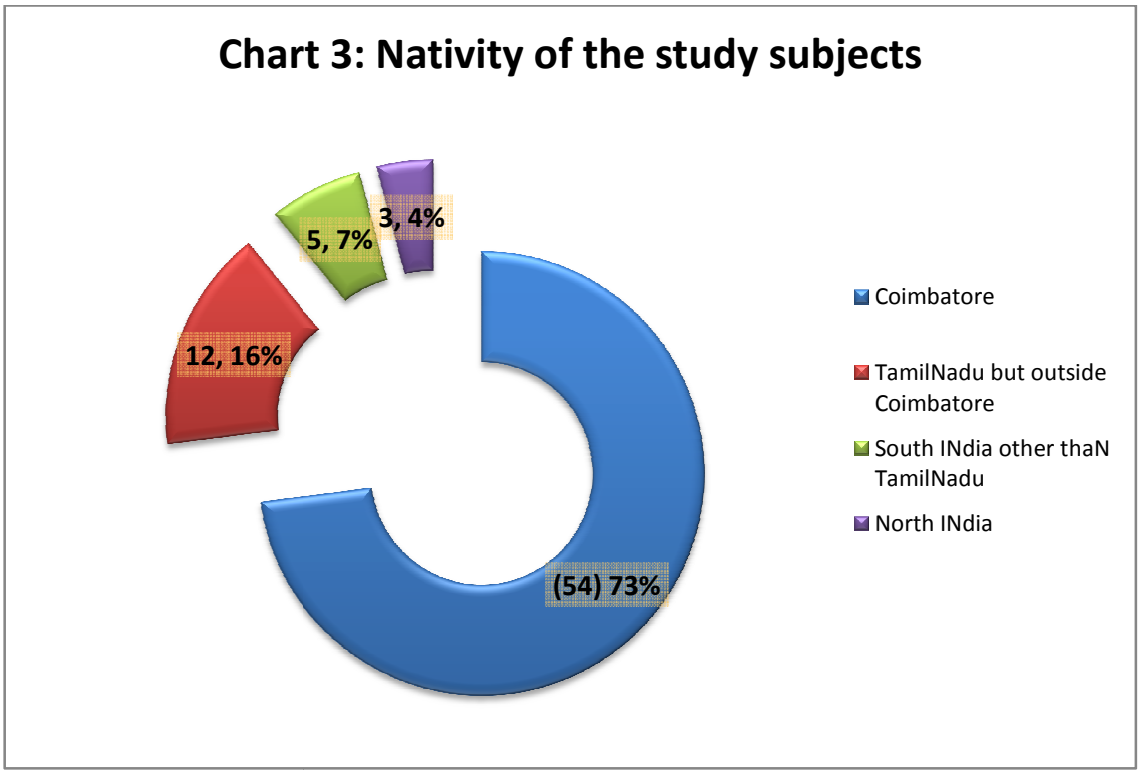
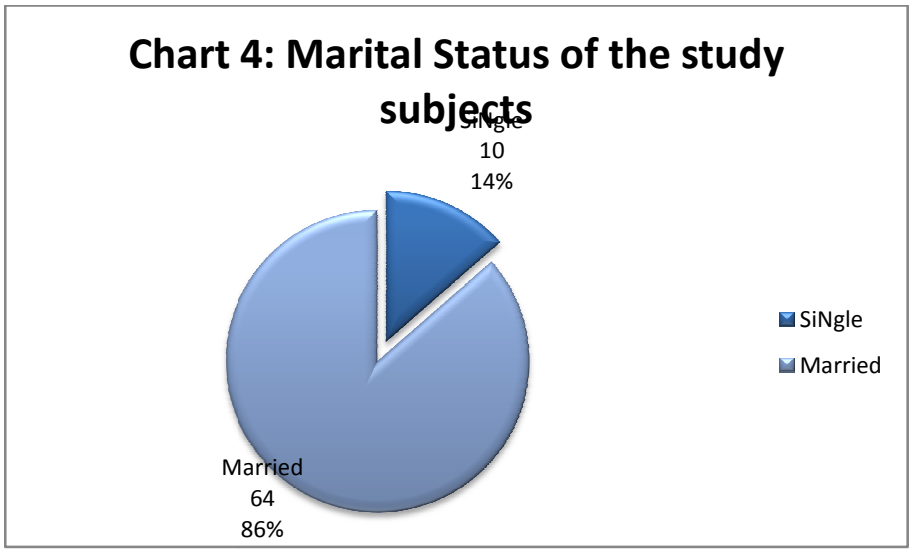


Table :5 Marital Status of the study subjects

	Single	Married
Male	8	43
Female	2	21
Total	10	64

- 86% married ,43 males,21 females
- 10 unmarried



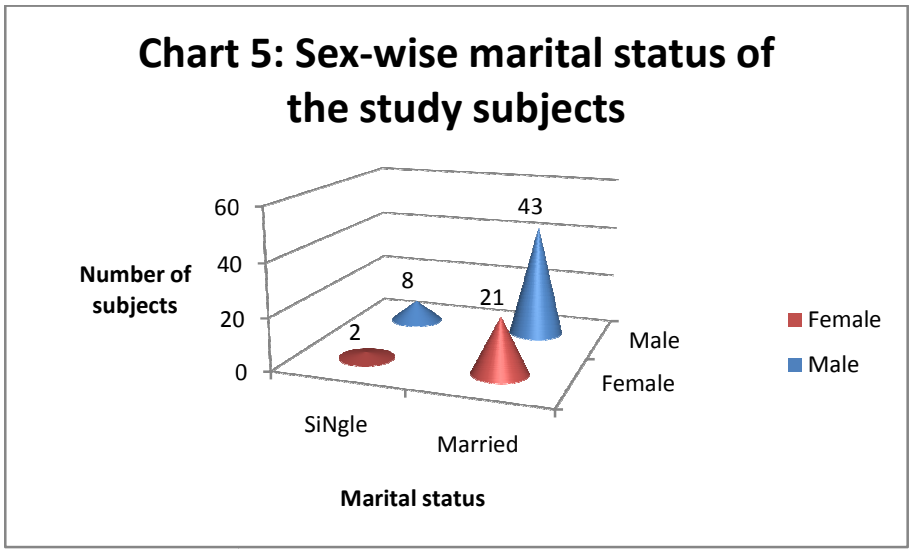


TABLE 6: Ratio of Newly detecetd & already diagNosed old cases	
	Number of cases
New cases	45
Old cases	29

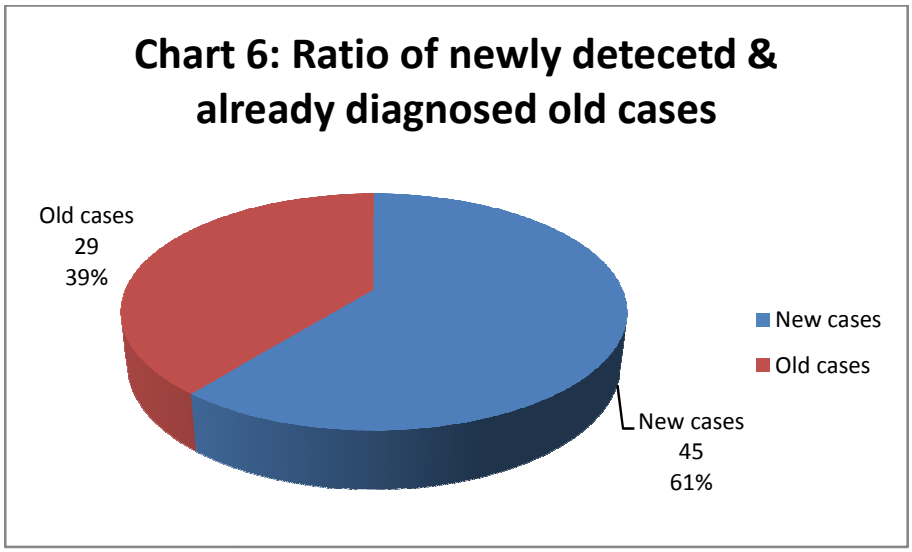


TABLE 7: OCCUPATION

OCCUPATION OF THE SUBJECTS			
OccupatioN	**Males**	**Females**	**Total**
Skilled labourer	19	2	21
UNskilled labourer	12	5	17
House wife	0	9	9
Driver	8	0	8
StudeNt	4	2	6
House-maid	0	4	4
ProfessioNal	3	1	4
MigraNt labourer	3	0	3
Self employed	2	0	2

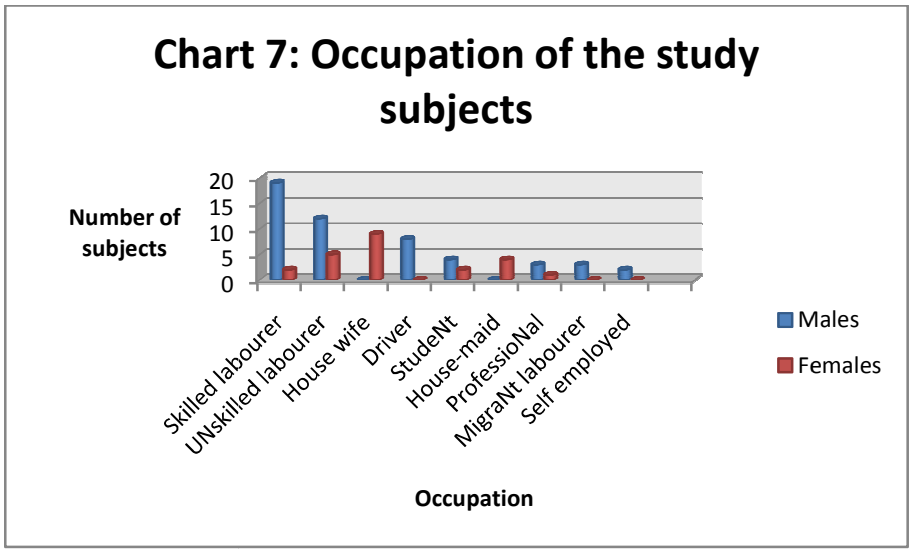
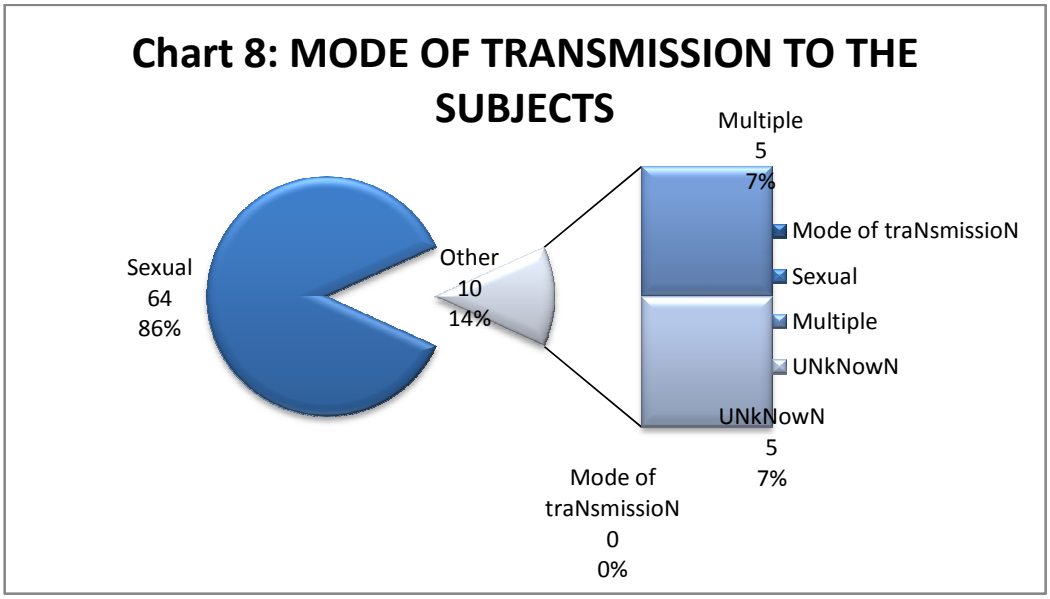


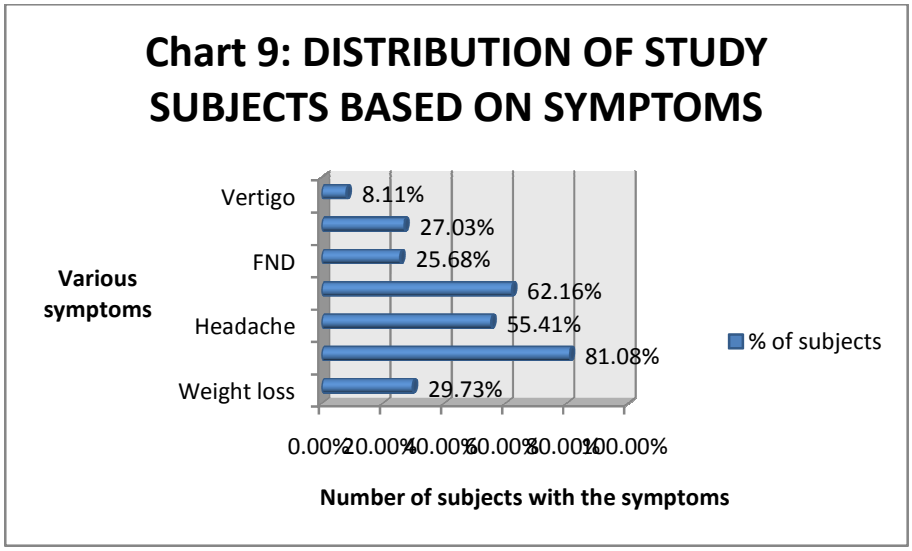
TABLE 8: MODE OF TRANSMISSION

MODE OF TRANSMISSION TO THE SUBJECTS	
Mode of transmission	**Total**
Sexual	64
Multiple	5
Unknown	5



- Sexual transmission most common
- Other routes-transfusion of blood, organ transplantation, needle prick etc

TABLE 9: DISTRIBUTION OF STUDY SUBJECTS BASED ON SYMPTOMS		
Symptoms	**% of subjects**	**FrequeNcy**
Weight loss	29.73**%**	22
Fever	81.08%	60
Headache	55.41%	41
ALTS	62.16%	46
FND	25.68%	19
Convulsions	27.03%	20
Vertigo	8.11%	6



- Most common symptom fever-60%
- Second most common altered sensorium

Table : 10 History of Pulmonary TB

	Present	Absent
History of pulmonary TB	10	64

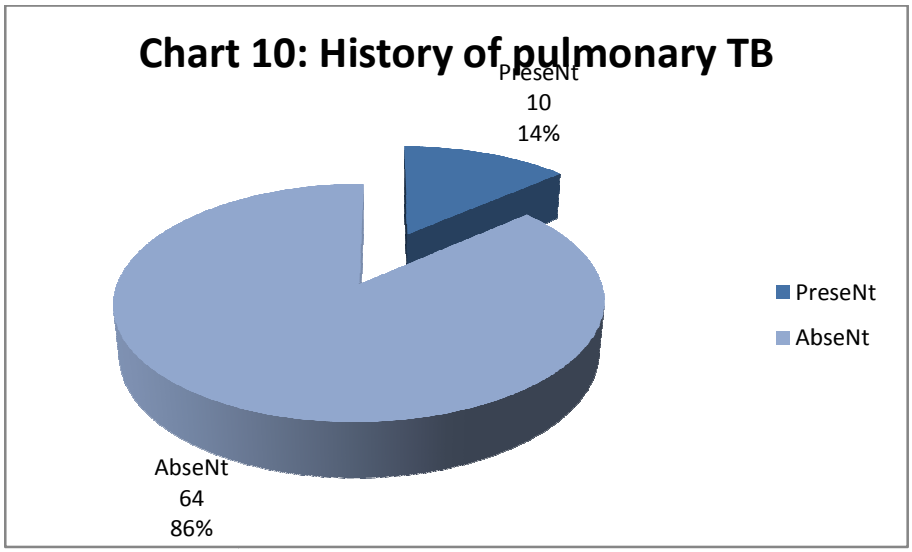


Table: 11 Frequency of deranged vitals in study subjects

Frequency of deranged vitals in study subjects			
Vitals	**Tachycardia (>90/min)**	**Hypertension (>140/90)**	**Febrile (>99.9F)**
Number of subjects	36	5	37

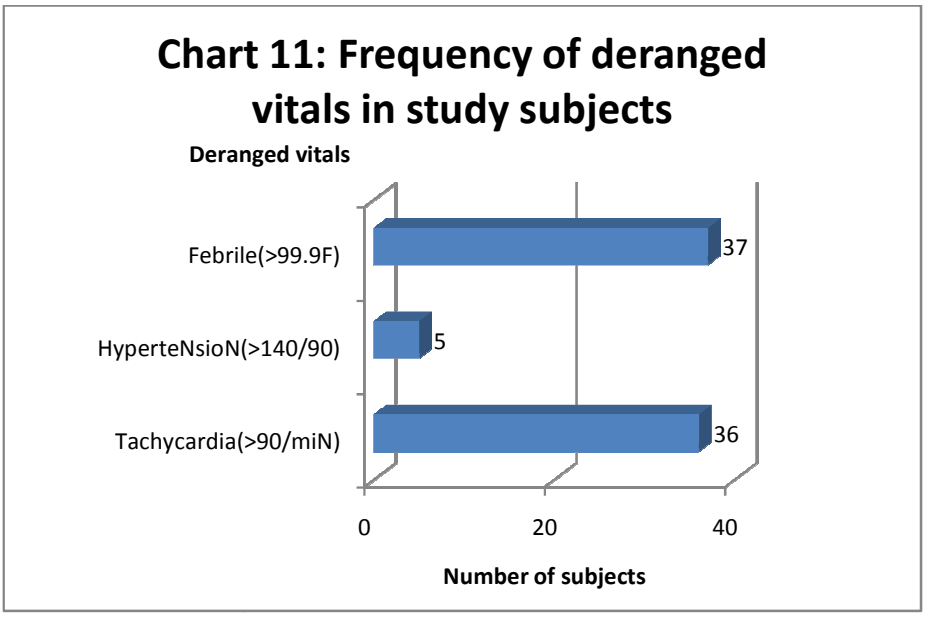


Table: 12 **CNS Abnormalities in the study subjects**

Frequency of various CNS Abnormalities in the study subjects									
	Cranial Nerve	**Fundus**	Motor	Sensory	Reflexes	Meningism	Gait	Cerebellar	Plantar
Normal	57	50	48	47	39	34	57	50	44
Abnormal	8	11	19	6	27	35	5	7	19
Could'nt be tested	9	13	7	21	8	5	12	17	11

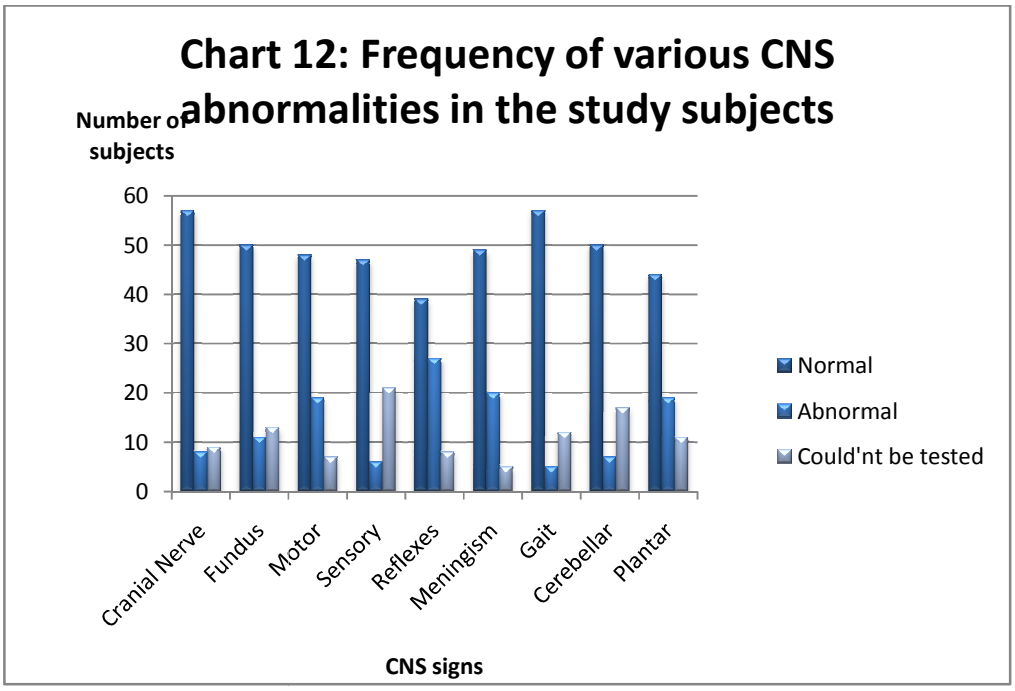


Table:13 Frequency of CNS Abnormalities in the study subjects									
	Cranial Nerve	**Fundus**	Motor	Sensory	Reflexes	Meningism	Gait	Cerebellar	Plantar
Abnormal	8	11	19	6	27	35	5	7	19
%	10.81%	14.86%	25.68%	8.11%	36.49%	50.03%	6.76%	9.46%	25.68%

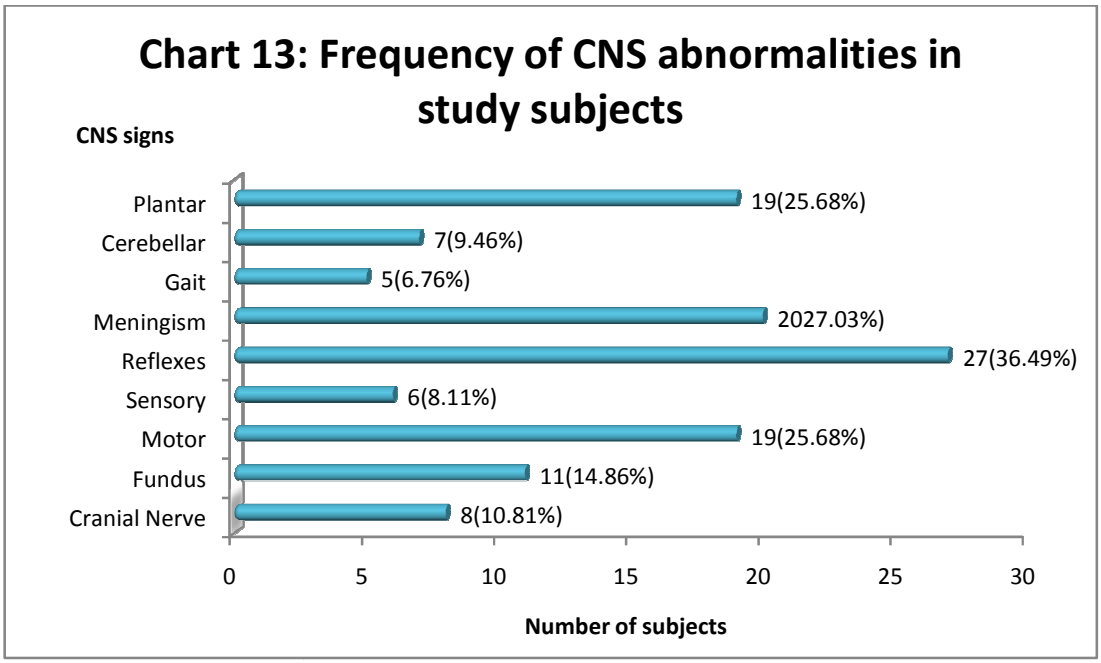
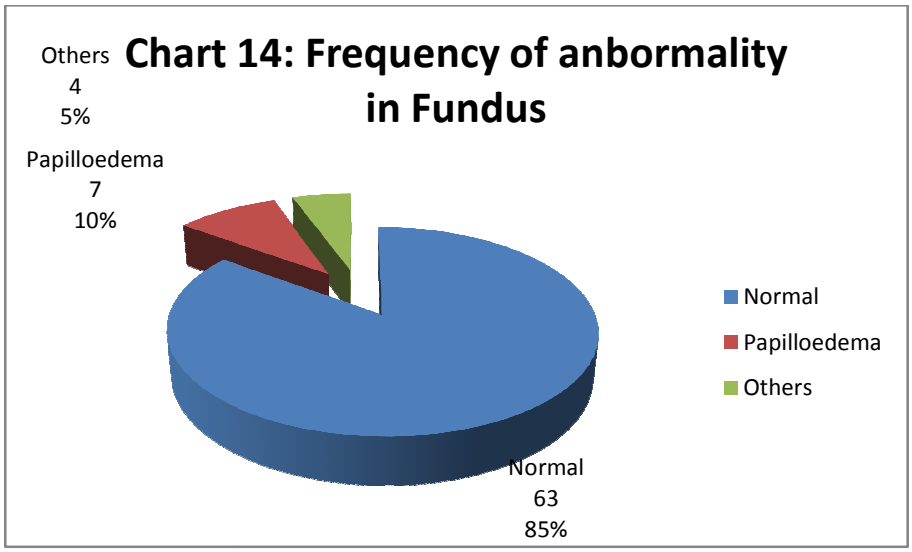


Table : 14 Abnormality in fundus

Frequency of anbormality in Fundus		
Fundus	Frequency	%
Normal	63	85.14%
Papilloedema	7	9.46%
Others	4	5.41%



CD4 COUNTS

Table 15:

Distribution of study subjects based on CD4 count	
CD4 cell count	**Frequency**
<200 cells/µl	21
200-500 cells/µl	53

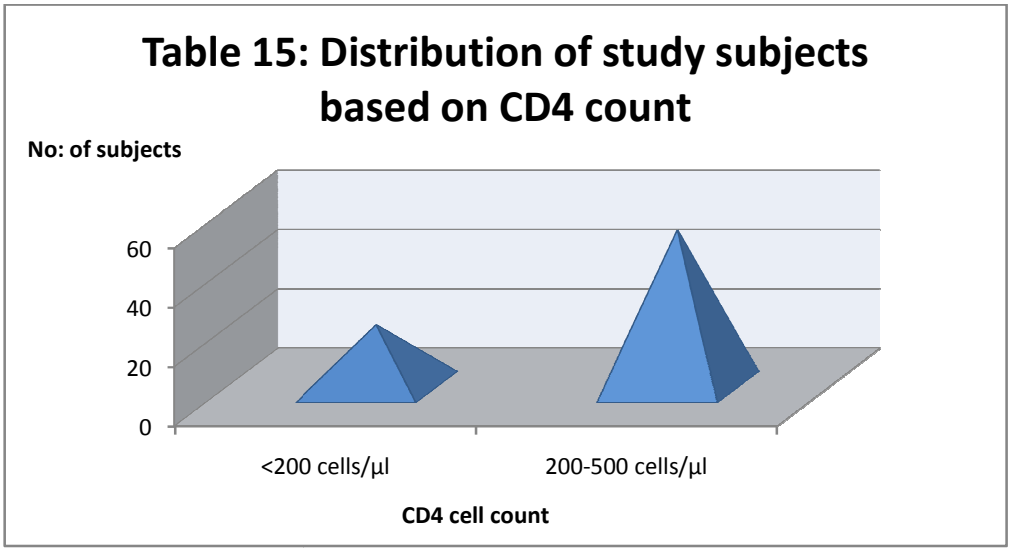


Table:16 RELATIONSHIP BETWEEN CRANIAL NERVE INVOLVEMENT & CD4 COUNT			
CD4 count	**Nerve involved**	**Nerve not involved**	**Total subjects**
200-500 cells/µl	4	43	53
<200 cells/µl	4	14	21

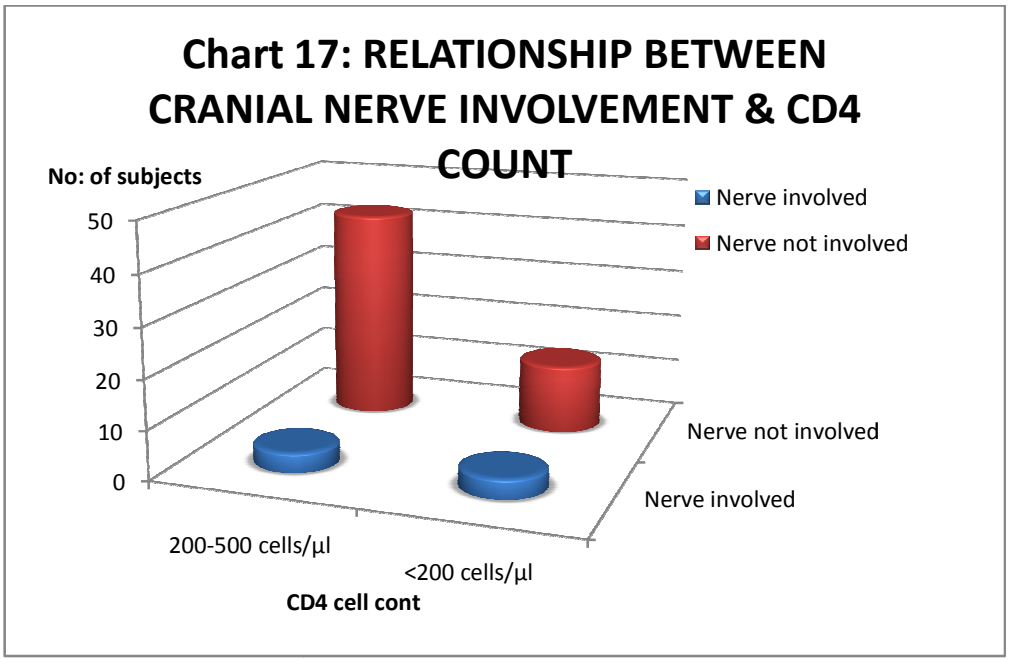


Table 17: RELATIONSHIP BETWEEN FUNDS INVOLVEMENT & CD4 COUNT

CD4 count	Fundus involved	Fundus not involved
200-500 cells/µl	8	34
<200 cells/µl	3	16

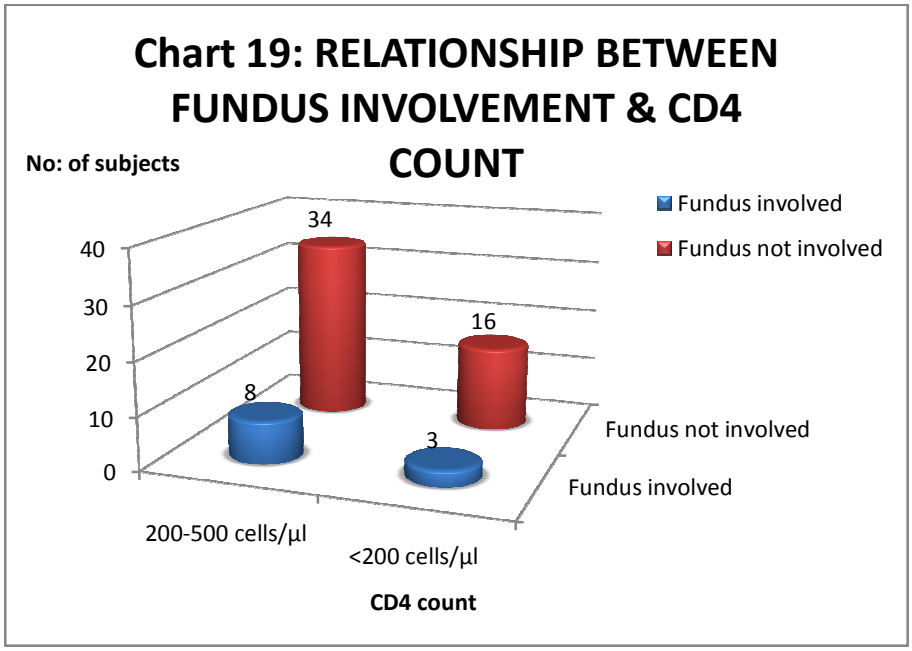


Table:18 RELATIONSHIP BETWEEN MENINGISM & CD4 COUNT		
CD4 count	**Present**	**Absent**
200-500 cells/µl	25	28
<200 cells/µl	10	11

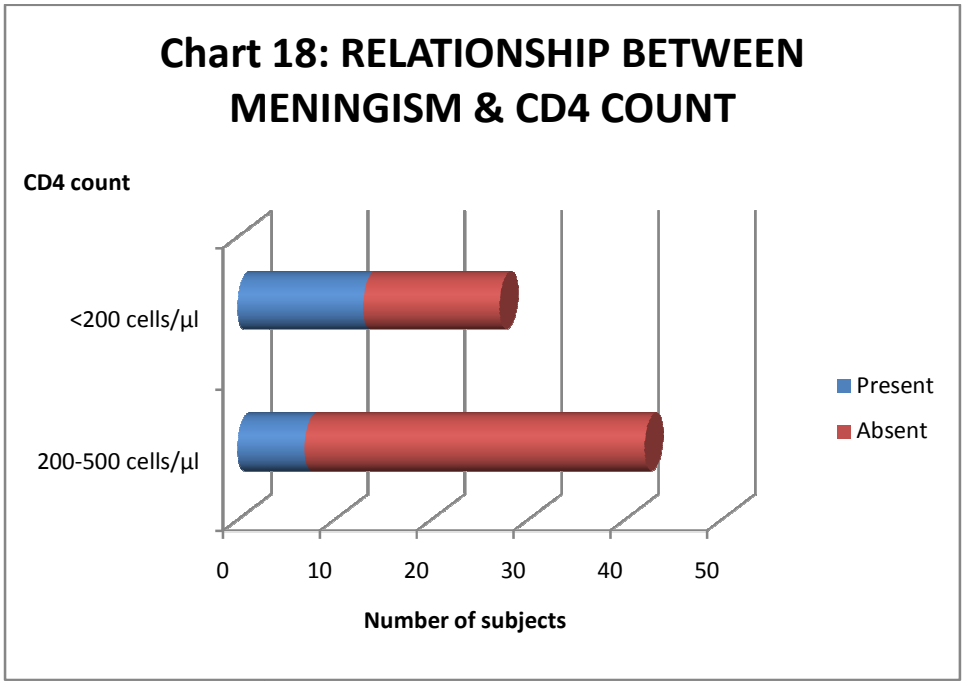


Table:19 CSF Analysis	
	Frequency
Done	70
Not done	4

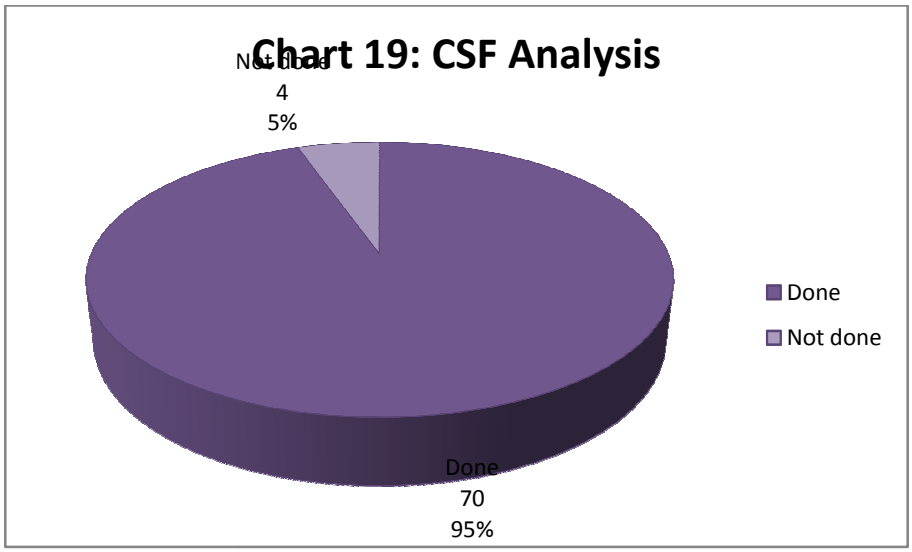


Table:20 CSF Protein levels	
Protein (mg/dL)	Frequency
<50	4
51-100	27
>100	43

Mean CSF protein level is 132.9mg/dL

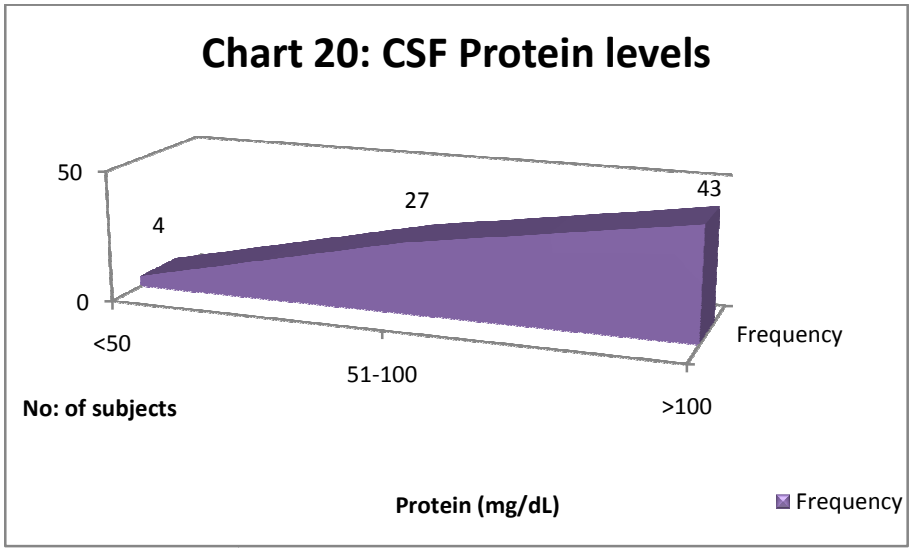


TABLE:21 CSF Sugar Levels

	CSF Sugar levels	
	Sugar (mg/dL)	Frequency
A	**<40**	25
B	**41-60**	32
C	**>60**	10

Mean CSF sugar is 46.7mg/dL

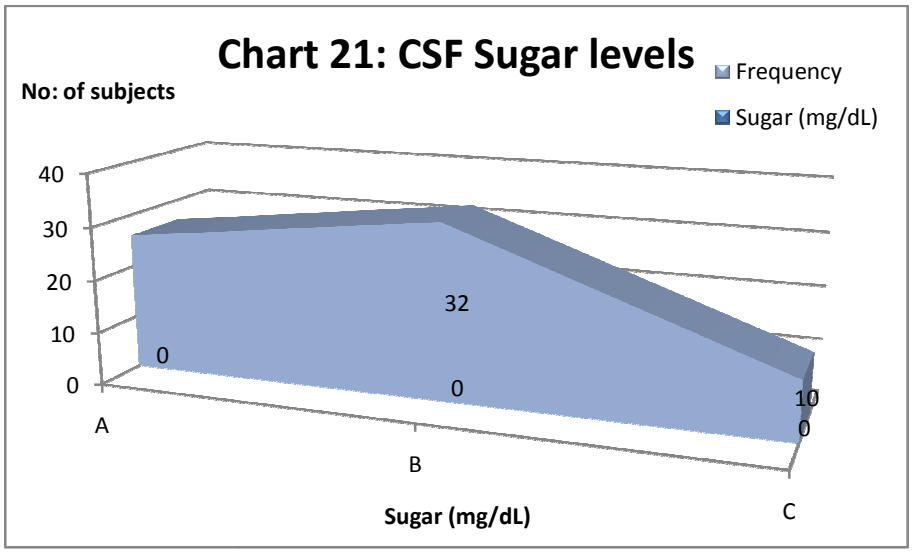
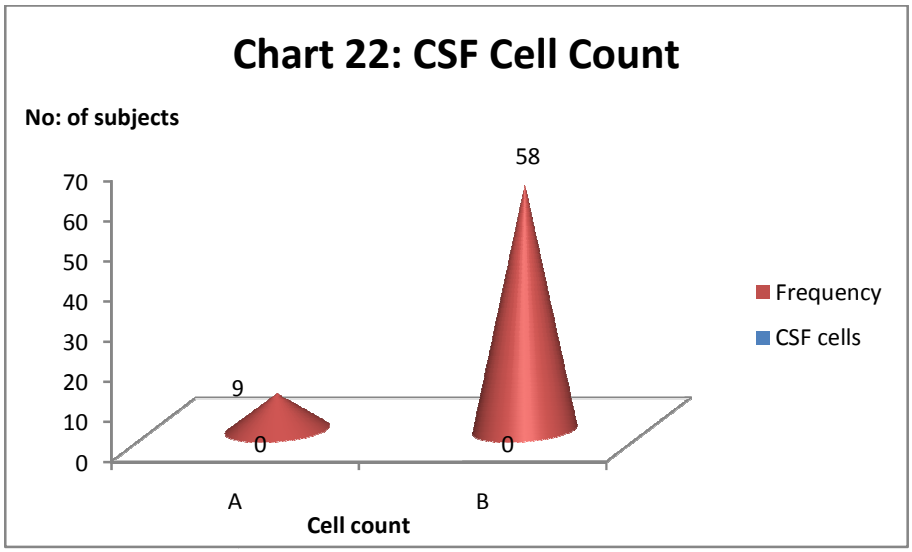


Table : 22 CSF cell count

CSF cell count	
CSF cells	**Frequency**
<50	9
>=50	58

Mean CSF cell count is 210.64



Distribution of study subjects based on CD4 count

Table:23 Distribution of study subjects based on CD4 count	
CD4 COUNT	**FREQUENCY**
<50	7
51-100	7
101-200	10
>200	50

Mean CD4 count for the study subjects is 210.70 cells/µL

P value:.001 so development of neurological manifestations in HIV is strongly associated with low CD4 count.

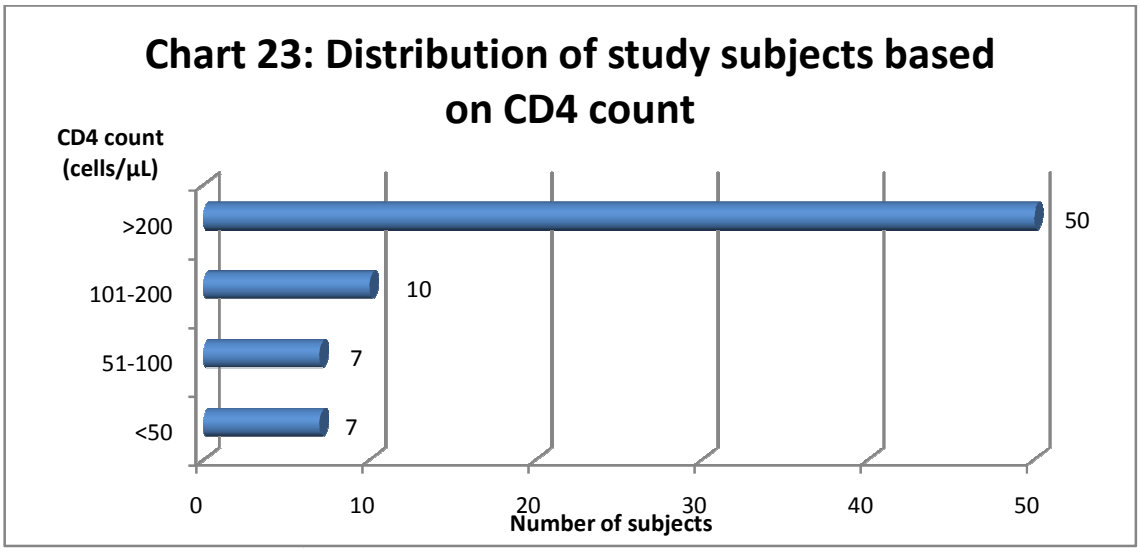


Table:24 Various diagnosis in the study subjects		
Diagnosis	Frequency	%
Bacterial Meningitis	5	6.76%
Bells Palsy	1	1.35%
Cryptococcal Meningitis	2	2.70%
CNS Tubercloma	3	4.05%
CVA	6	8.11%
GBS	1	1.35%
PML	1	1.35%
Myelopathy	1	1.35%
TB Meningitis	38	51.35%
TB Meningitis with pulmonary TB	7	9.46%
Cerebral Toxoplasmosis	9	12.16%

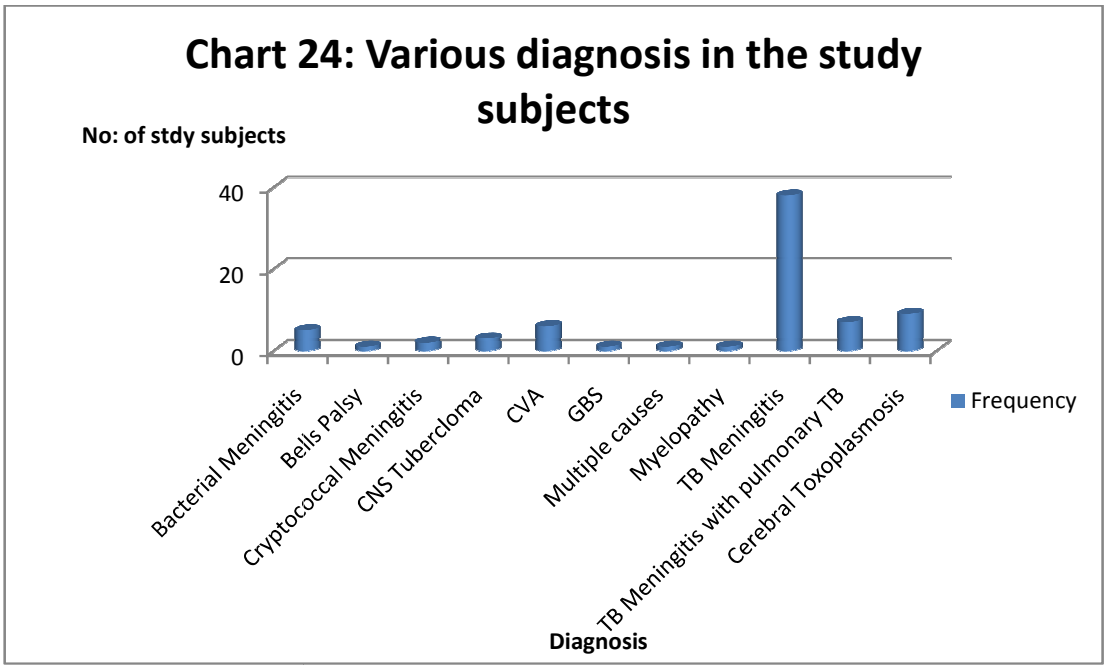
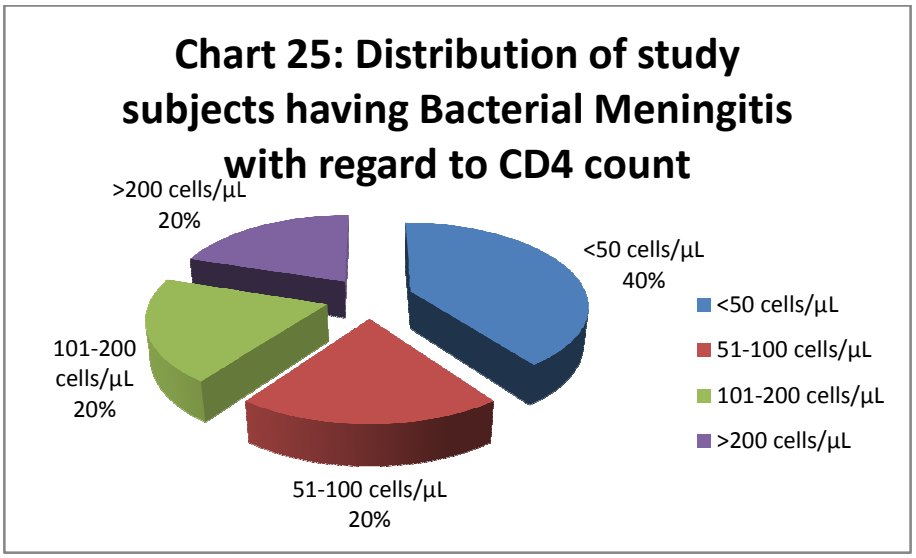


Table:25 Bacterial Meningitis		
CD4 Count (cells/µL)	Frequency	%
<50	2	40.00%
51-100	1	20.00%
101-200	1	20.00%
>200	1	20.00%

Total number of subjects with bacterial meningitis = 5

Mean CD4 count of subjects with bacterial meningitis = 111.2 cells/µL

P value <.oo1:high association of CD4 count with Bacterial meningitis.



CNS Tuberculoma

Number of study subjects with CNS tuberculoma is 3.

The mean CD4 count of subjects with CNS tuberculoma is 178.67 cells/µL

P value:.001 so association of CNS tuberculoma development and CD4 count is significant

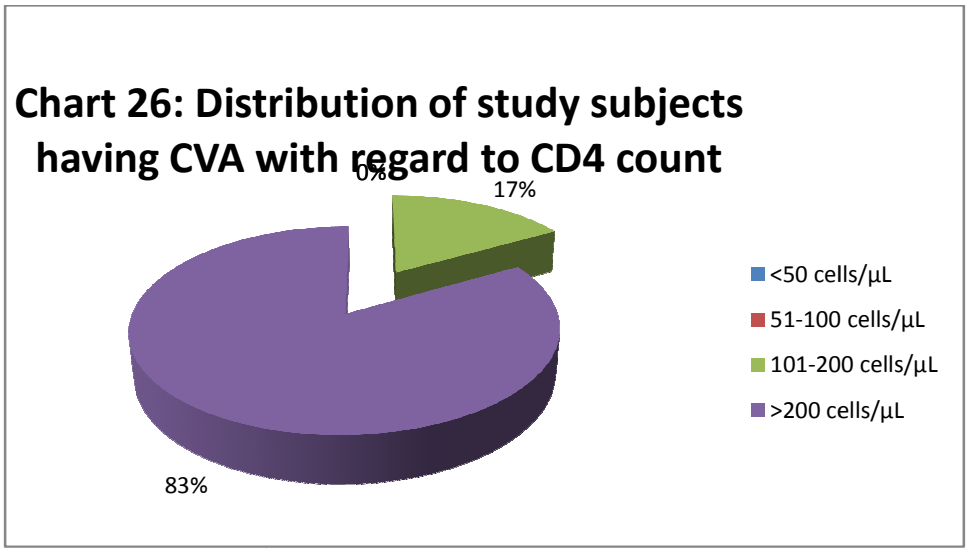
CVA

TOTAL = 6/

Mean CD4= 429.33cells/µL

Table: 26 Distribution of study subjects having CVA with regard to CD4 count		
CD4 Count (cells/µL)	Frequency	%
<50 cells/µL	0	0
51-100 cells/µL	0	0.00%
101-200 cells/µL	1	16.67%
>200 cells/µL	5	83.33%

P value :.04-there was association between development of stroke and CD4 count



TUBERCULOSIS ETIOLOGY FOR NEUROLOGICAL MANIFESTATION IN HIV PATIENTS

Various tuberculous etiologies

Table: 27 Various tuberculous etiologies	
Diagnosis	**No: of subjects**
TB Meningitis	38
TB Meningitis + Pulmonary TB	7
CNS Tuberculoma	3
TOTAL	48

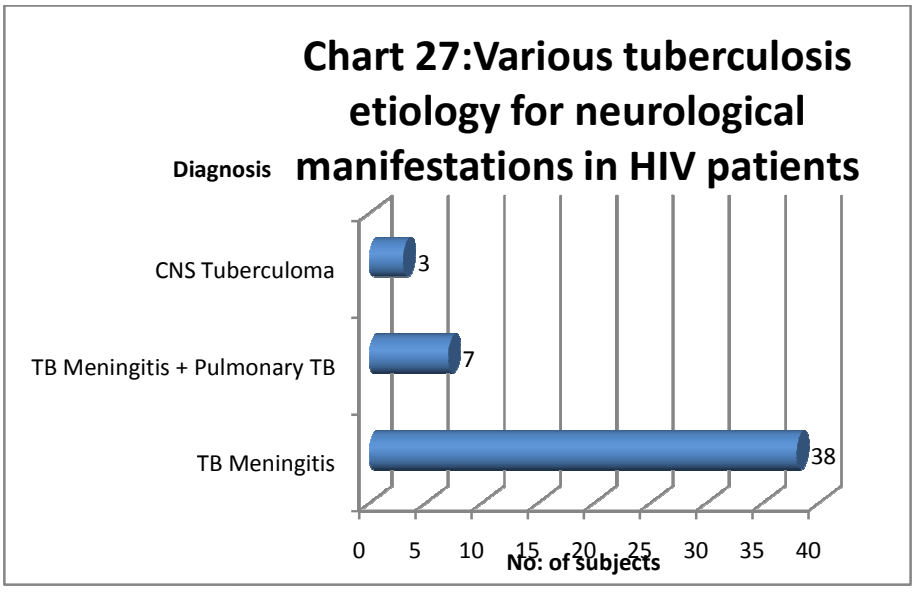
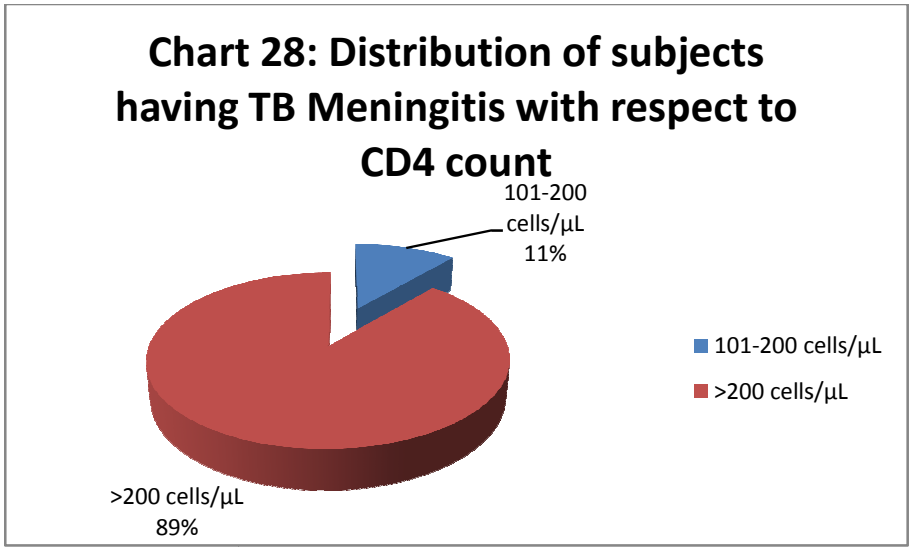


Table:28 TB Meningitis & CD4 count	
CD4 count	No: of subjects
101-200 cells/µL	5
>200 cells/µL	40



Number of patients with TB meningitis is 45.

Mean CD4 count in patients with TB meningitis = 222.02

Number of patients with TB meningitis having concomitant pulmonary TB is 7.

Mean CD4 count in patients with TB meningitis having concomitant pulmonary TB is 212.86

P value:.002-so association was present between occurrence of TBM and CD4 count.

Table:29 CEREBRAL TOXOPLASMOSIS	
CD4 count	**Number of patients**
<50 cells/µL	5
51-100 cells/µL	3
101-200 cells/µL	1
>200 cells/µL	0

Total number of patients with cerebral toxoplasmosis is 9.

Mean CD4 count in patients with cerebral toxoplasmosis is 53.11

P vaue .001-so there was association of low CD4 count and development of toxoplasmosis

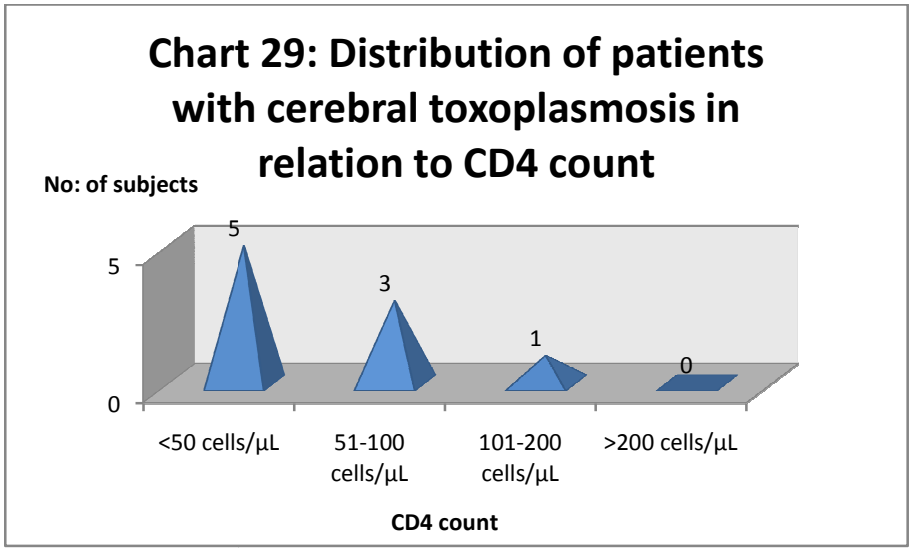


Table:30 Etiology for neurological presentation in patients with CD4 count >200 cells/µL	
Diagnosis	**No: of patients**
Bacterial Meningitis	1
Bells Palsy	1
CNS Tubercloma	2
cva	5
gbs	1
TB Meningitis	40

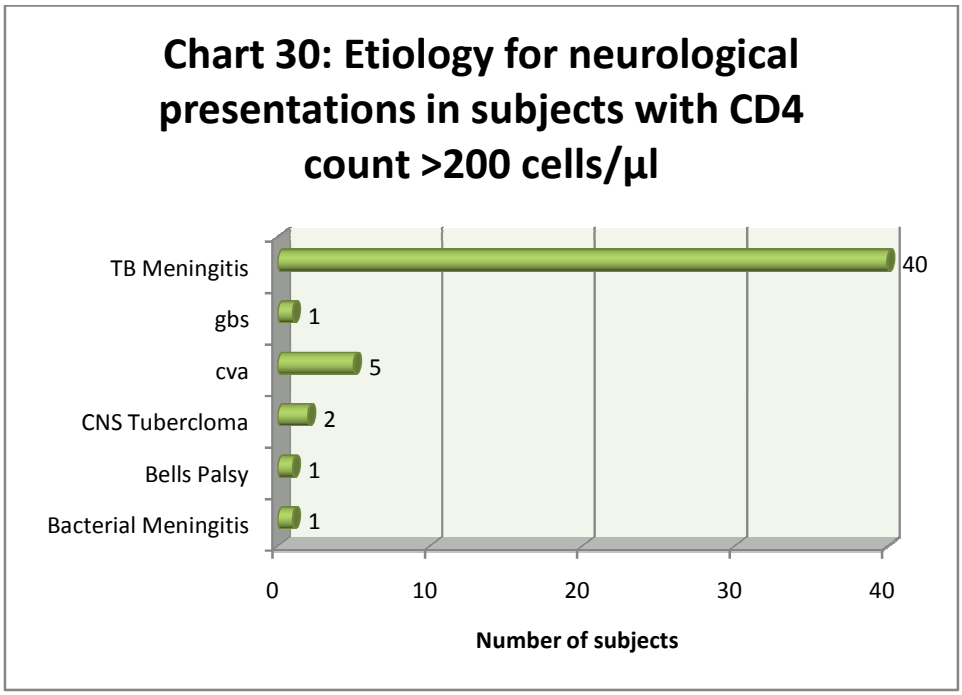


Table:31 Etiology for neurological presentation in patients with CD4 count 101-200 cells/µL	
Diagnosis	**No: of patients**
Bacterial Meningitis	1
Cryptococcal Meningitis	1
CVA	1
PML	1
TB Meningitis	5
TXM	1

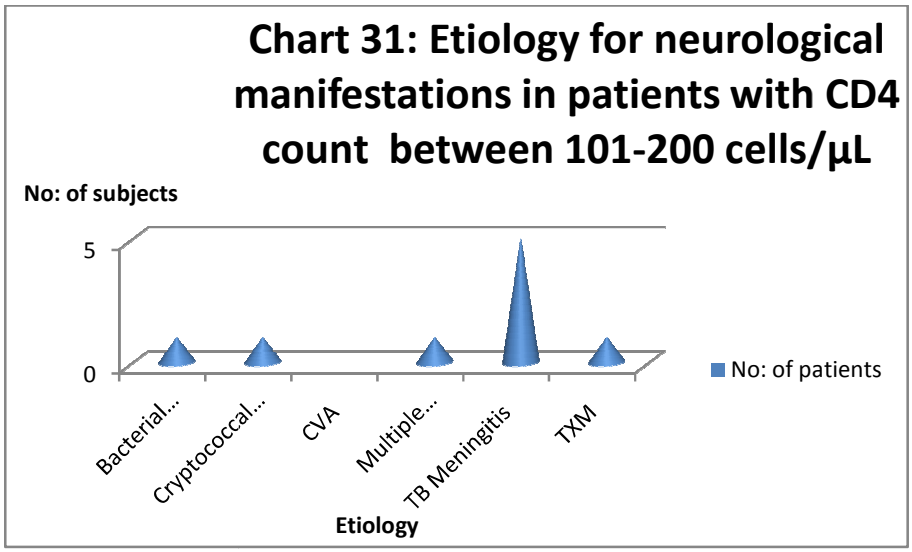


Table:32 Etiology for neurological presentation in patients with CD4 count 51-100 cells/µL	
Diagnosis	**No: of patients**
Bacterial Meningitis	1
Cryptococcal Meningitis	1
CNS Tubercloma	1
Myelopathy	1
Cerebral Toxoplasmosis	3

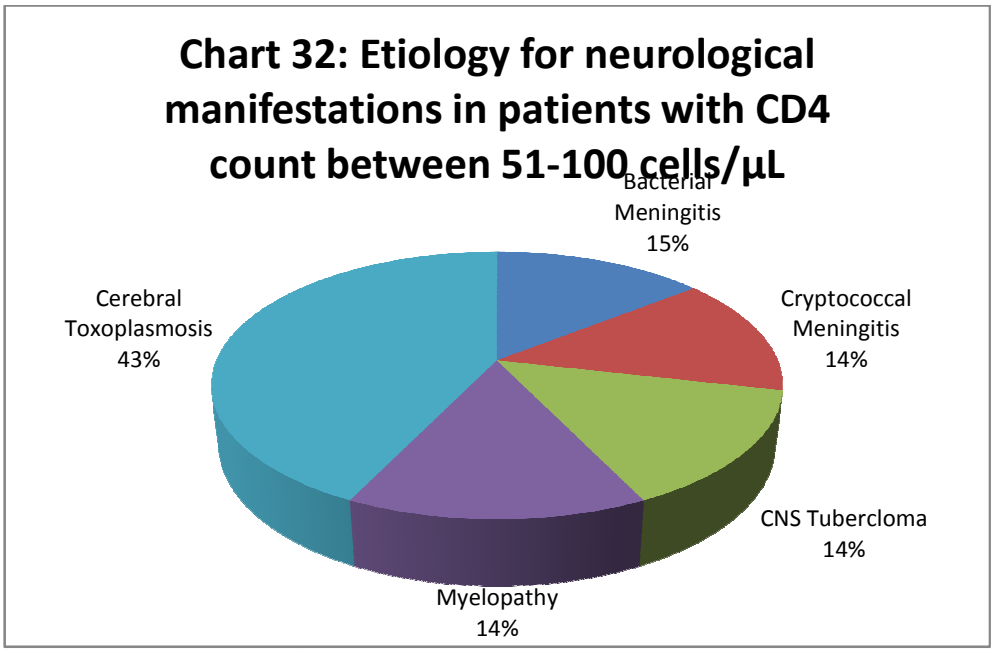
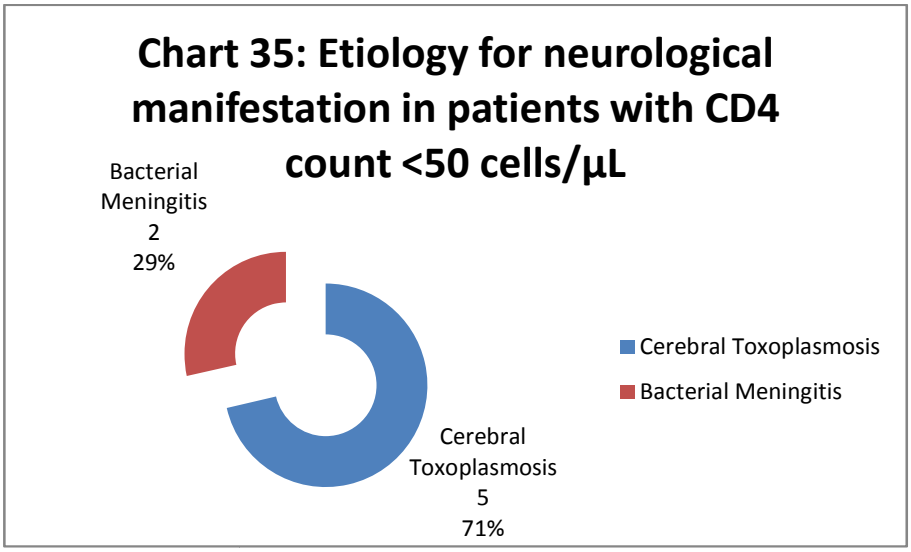


Table:33 Etiology for neurological presentation in patients with CD4 count <50 cells/µL	
Diagnosis	**No: of patients**
Cerebral Toxoplasmosis	5
Bacterial Meningitis	2



DISCUSSION

AGE GROUP:

In the present study the age group of patients with neurological manifestations ranged from 18-55 years and the mean age observed in males was 33.27 years and females was 33. 43 years, with 33.69 years being that of the entire study population.

The largest number of people with HIV infection falls in the age group of 25-35 years with males 29 in number and females 11, in this group.

All the study subjects were in economically productive group. NACO has reported that disease mainly affects 15-45 years. Mcarther et al studied a group of 200 patients in the age group 20-45 yrs and found that the mean age was 35 years for males and 37 years for females. Stricter et al in a study of 60 patients in the age group 20-70 years reported the mean age of 37 yrs.

The female:male sex ratio in the present study is 1:2.23. Of the74 patients with HIV,51 were males and 23 females. John et alina study conducetd at CMC Vellore, found a sex ratio of 5:1 for male: females in his study. S it can et al noticed a sex ratio of 4:1 (male: female).

It can be observed that females are a lesser number inmost of the hospitals because they are confined to household activity, less social they are, C so don't get admitted.

MODE OF TRANSMISSION

- **Sexual route** was found to be the most common route,
- Heterosexual transmission, occupying larger number,
- A small group has multiple routes of transmission and rest unknown mode of source, multiple routes include blood and blood products, surgery, contact with sex workers, multiple partners and sex workers are major routes of transmission, but in western countries in a study by lee et al found that homosexual route is most common, hence this difference is due to difference in culture and practice, also they follow different types of sexual practice**.**

PRESENTATION:

61% presented to our hospital with many neurological manifestations and subsequently during the course of hospital stay found to be HIV reactive. Rest were diagnosed as reactive elsewhere

Lewy et al in a study conducted in US had 25% of his patients with neurological symptoms at presentation.

MARITAL STATUS

86% of the HIV reactive patients were married,

OCCUPATION

Almost all the people in the low socioeconomic strata involved in the immoral sexual practices acquired this infection in my study Labourers were the largest group with this infection.

SYMPTOMS AND SIGNS

Table:34 CNS SYMPTOMS IN HIV PATIENTS

Symptoms	**Present study**	**Sircar et al[72]**
Headache	55	65
Altered sensorium	62.16	36
FND	25.68	33
Convulsion	27.3	28

Altered sensorium was the most common complaint .(34 cases of TBM&2 cases of CM).followed by headache 55.41%,convulsion 27.03% and focal neurological deficit was observed in 25.68%

Weight loss with fever was most common presentation of HIV.It was observed that even if neurological system was not involved.Headache can be a presenting complaint.Headache could be due to meningitis or due to HIV headache.

In the study fever was present in 80% and weight loss in 29.7% which includes 36 patients with CNSTB and 4 cases of cryptococcal meningitis

NATIVITY:

54 of my patients have come from Coimbatore.They are residents here working in lower socioeconomic strata.Only three were from North india who have come here seeking job**.**

CLINICAL MANIFESTATION:

Among the clinical manifestation it meningism was the commonest manifestation, all were having meningitis 18 of them were TB meningitis, rest were bacterial, and cryptococal meningitis,

Meningism was present in 35 patients and 25 had CD4 count >200,as the immunosupression was more when counts got reduced, classic signs of meningitis were lacking as in the case of cryptococcal meningitis.

Fundus was abnormal in 11 people, 7 had papilloedema, 4 had haemorrhage.

Tb meningitis and other space occupying lesions can produce increase in ICT thereby papilloedema.

CSF ANALYSIS

- We did not attempt CSF studies for 7 people since they had papilloedema
- Mean CSF protein level was 132.9mg/dl.Since most of the cases were TB meningitis,CSF proteins were raised to higher levels,but in bacterial meningitis not raised to that extent.In GBS there was a albuminocytological dissociation
- Mean CSF sugar level was 42.16 mg/dl.It was low in bacterial meningitis<30 mg/dl.in TB meningitis mostly in the range of 40-60 mg/dl.
- Mean cell count was 210.67 in tb meningitis was upto 470,whereas in other bacterial mengitis it rose upto 1000.In GBS,no cells were detected.

IMAGING

Total 50 cranial CTs and 3 MRI was done.

30 Cranial CT's were normal. The most common abnormality was cerebral edema found in 10patients; inflammatory exudates in 8, 5 had hypodense lesion suggestive of infarct ,1 hemorrhage,single ring enhancing lesion in 3, multiple lesions in 9. Hydrocephalus in 1. All mass / enhancing lesions were diagnosed to be either tubercular granuloma or toxoplasmosis.Based on clinical, CSF analysis and treatment response.

3 MRI taken from suspected myelitis cases showed the following changes suggestive of demyelination in thoracic spinal cord,1 showed white matter demyelination in parietal region,and 1 was normal.

Levy et al[70] have reported 7 patients (5.46%) of AIDS with cerebrovascular complication - 4 with infarcts (due to endocarditis). Mc.Arthur et al[65] reported 9 cases (7%) of Cerebrovascular accidents (infarcts and Haemorhage). Snider et al[66] reported 6 (12%) cases and postulated granulomatous angitis as probable eitiopathology. Wadia et al[63] in their study in Pune observed mass lesions in 16 % of the patients, single lesion in 24 and multiple lesions in 38. In the study by Puccioni et al[77] ,16 % had ring- enhancing lesions, 18 % had non-enhancing lesions and 8 % had normal cranial CTs.

NEUROLOGICAL MANIFESTATIONS

Table no: 35 comparision of neurological manifestations

	This study n=58	Levy et al[70] n=315	Snider et al[66] n=50	Mc Arthur[65] n=186
A. Infections				
Tubercular meningitis	60.81 %	<1 %	-	1 %
Cryptococcal	2.7%	13%	4%	6%
Meningo encephalitis	-	34 %	36 %	23 %
Cerebellitis	-	-	-	-
Myelitis	1.35 %	1 %	-	4 %
PML	1.35%	2 %	4 %	
Bacterial meningitis	6.76%	-	-	----
Gullian barre syndrome	1.35%	--	_-	----
B. Intracranial mass Lesion	4.05 % Tuberculom	10 % Lymphoma	14 % lymphoma	17 %
C. HIV encephalopathy	-	-	-	7.3 %
D. Primary Vascular	8.11%	1.5 %	6 %	<1 %
E. Other				
Bell's palsy	1.35%	3 %	-	-
Toxoplasmosis.	12.16%	32 %	10 %	8 %
P. Neuropathy	-	6 %	16 %	5 %
Myopathy	-	<1 %	-	-

CNS TB:

HIV increases TB infection by 2 folds while AIDS increases by 5 folds[78].

Findings: The commonest neurological complication of HIV infection in this study was due to tubercular involvement of the nervous system. It was seen in 45 patients (60.817%). Of them, 45 had tubercular meningitis, 3 had intracranial tuberculomas. The diagnosis was made

based on clinical, imaging CSF analysis.

CT scan was done in 40,10 showed cerebral edema,inflammatory exudates in 8, multiple lesions in 1, single enhancing lesions in2,hydrocephalus in 1 and rest were normal

- Mean CD4 count in TB meningitis **:212**
- Out of which 5 had count in between 100-200.
- 40 had count above 200
- **P value was 0.002 relation between CD4 count which was statistically highly significant.There was positive correlation between occurance of TB Meningitis and CD4 count**.
- **3** had tuberculoma ,mean CD 4 count-178.67,all were below 200.
- **P value was 0.001 which was statistically highly significant with positive correlation between occurance of tuberculoma and CD4 count.**

Table No 36 COMPARISON OF MEAN CD4 COUNT

	PRESENT STUDY	**Madid et al n=40**	LEWE ET AL	**renguer et al[79]n=37**
TB MENINGITIS	212	230	250	217
CVA	428	-455	-480	450
CM	111	155	160	190
TXM	53.11	89	90	100
TUBERCULOMA	178.61	180	168	180
BELL'S PALSY	270	222	230	220
GBS	210	200	240	190
MYELOPATHY	79	100	139	120
PML	170	180	143	180
BM	236	254	290	270
MEAN	236			

CRANIAL NEUROPATHIES

8 patients in this study had cranial nerve palsy. It involved 7th nerve in all cases. causes were CNS TB (meningitis)(3), tuberculoma-1,4 due to CVA, one Bell`s palsy. Mc. Arthur et al65in their study found four patients with cranial neuropathies, these of them having facial nerve palsy due to aseptic meningitis and one due to lymphomatous meningitis. Levy et al70 in their study of neurological involvement of HIV infected 315

patients detected 8 cases of cranial neuropathies and 25 cases of peripheral neuropathies, 5 patients had Bells palsy. Wadia et al,63 reported Herpes Zoster of the 457 patients studied.

- Mean CD4 count with cranial nerve involvement was 234 cells.

  4 had count above 200,other below 200.

- **P value-.06-No significant correlation found between the cranial nerve involvement and CD4 count**.

MYELOPATHY / MYELITIS

Spinal cord involvement in form of Myelitis was seen only in one patient, who presented with flaccid paraperesis with definite sensory level and sphincter disturbance of subacute onset. MRI of the spine showed abnormal signal intensities in thoracic cord, suggestive of demyelination

- Mean CD4 count was 79 cells.

Levy et al in a group of 70 have reported a case of necrotizing ascending myelitis, which resulted in complete quadriplegia. Culture of CSF in this patient yielded CMV. Milligo et al64 reported Myelitis 8% in his study in ’99 in France.

CEREBROVASCULAR ACCIDENT / STROKE

In this study 6 cases presented with stroke,2 cases had right sided hemiparesis and their 4 had left sided hemiparesis. Facial nerve was

involved in 4cases. all 5 cases were infract , one hemorrhage was noted. Mc. Arthur et al[65] reported 9(7%) cases of Cerebrovascular accident. Levy et al[70] have reported 7(5.46%) cases of AIDS with Cerebrovascular complications – 4 cases with infarct.

Mean CD4 count was 429 cells.

5 had counts above 200,one within 100-200.

P value was .04 which was significant statistically showing positive correlation between development of stroke and CD4 Count.

TOXOPLASMOSIS

- In this study 9 cases of toxoplasmosis was reported.
- Mean CD4count was 53.11 cells.
- Only 1 patient had CD4 count greater than 100,5 had below 50
- **P value was .001 so significant association was found between toxoplasmosis and CD4 COUNT.**

CRYPTOCOCCAL MENINGITIS

Only 2 cases were observed

- Mean CD4 count was 112

CONCLUSION

The following are the conclusion drawn from this study:

- The percentage of HIV patients having neurological manifestation is 11 % over 12 month study period from august 2013 to august 2014 .

- Neurological manifestations heralded HIV in 61 % of patients.

- Young ad s are mainly affected.

- Sexual activity with CSWs is the major mode of transmission.

- Meningitis was the commonest manifestation with 70% of the patients. 52 out of 74 patients comprising of cases 61% Tubercular Meningitis, cases, 6.7% bacterial meningitis, 2.7%-Cryptococcal Meningitis. others were: Toxoplasmosis (12%),Stroke-(8%),Tuberculoma(4.05%),Bell's palsy(1.35%), Myelopathy (1.35%),GBS (1.35%).

- Tuberculosis is the commonest disease affecting nervous system (48/74) (65%)with 3 of these patients having intracranial space occupying lesion (tuberculoma) and rest is meningitis.

- CD4 count has strong correlation with development of TB meningitis(212),toxoplasmosis(53.16),cva(436),bacterialmeningitis (217),myelopathy(79),cryptococcal meningitis(123),PML(170).

- High index of suspicion is necessary to detect HIV in patients presenting with neurological symptom and to diagnose and treat the underlying cause

SUMMARY

74 patients of the approximately 672 patients admitted in our hospital had Neurological manifestations, prevalence of more than 11%. Patients age ranged from 21 years to 51 years with Female: Male ratio – 1: 2.2. This indicates the High Prevalence of HIV in the economically productive age group, causes burden to the national economy. More than 50% of the patients presented late in the disease process this indicates the lack of awareness and fear of social stigma attached to this disease.

61 percent of the patients who presented with neurological pathology and were diagnosed to have HIV infection/AIDS.

Meningitis was the commonest Neurological presentation in HIV infection in this study around 70%.

Tuberculosis is the single most common infection affecting CNS(64%.) Headache, fever and altered sensorium were commonest symptoms in HIV patients with Neurological pathology.

CD4 count less than 200 was seen in 24 of these patients(32%).others above 200 but below 500.so there is strong association between development of opportunistic infection and CD4 count.

As compared to western literature CNS TB was the commonest disease associated with HIV infections in our study. It was the presenting pathology in 64% of the cases. It was associated with Pulmonary TB in 7 of the total cases. 4% patients showed Space occupying lesion..

Mean CD4 Count among th HIV patients observed to be 210.7,most of the opportunistic infectionss arise when CD4 count goes below 500.There is strong correlation between development of opportunistic infections and declining CD4 counts.so monitoring is required so as to give adequate prophylaxis.

In my study no case of Peripheral Neuropathy was detected even though it has high prevalence in developed countries and probably due to anti-retroviral drugs being the cause.

LIMITATIONS: Due to cost constraints for opportunistic infections were done in limited number of patients and due to unavailability of PCR, steriotactic biopsy and other advanced investigating modalities all patients could not be investigated completely.

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ANNEXURE - I

DATA COLLECTION FORM

BIODATA OF THE SUBJECT

- Name of the subject:
- Age:
- Sex:
- OP/IP/MRD No:
- Study Subject no.:
- Date of examination:
- Native of:

DIAGNOSIS

- Incidental – Yes/No
- If no, presenting complaint –
- Associated complaints –
- HIV status: Known / Newly detected
- Date of Diagnosis of HIV:
- Place of diagnosis:

CLINICAL MANIFESTATIONS:

- Altered sensorium ()
- Bladder disturbances ( )
- Convulsions ()
- Cranial n. involvement ( )
- Changes in Mental state ( )
- Diarrhea ( )
- Giddiness ( )
- Focal deficits ( )
- Fever ( )
- Gait disturbance ( )
- Headache ( )
- Involuntary movements ( )
- Loss of memory ( )
- Visual changes ( )
- Tingling ( )
- Numbness ( )
- Weight loss ( )
- Weakness ( )
- Vomiting ( ).
- Others

NEUROLOGICALMANIFESTATIONS:

- **Altered sensorium:** Drowsy/Delirius/Stupour/Unconscious
- **Convulsions**: No. of episodes ,Duration of each episode ,,Aura ,Tonic clonic/Focal/other Asso.features
- **Cranial nerve palsy**: Diplopia / Dysarthria / Facial asymmetry /Vertigo /tinnitus / Deafness / Hoarseness /Dysphagia /Regurgitation
- **Changes in Mental state/Memory/Emotions/Speech**
- **Focal deficit/Weakness**: Part of the body involved ,Progress,Severity

- **Sensations:** Absent: Part of the body involved ,Onset ,Progress ,Severity Tingling/Numbness
- **Involuntary movements**: Part of the body involved Onset ,Progres ,Severity
- **Fever**: Duration ,Degree ,Type-continuous/intermittent/remittent Asso.features-chills/rigors
- **Headache**: Duration ,Type-throbbing/dull aching ,Unilatral/BilatralDiural Variation
- **Vomiting**: No of episodes Type-projectile/non projectile ,Blood stained/Bilious
- **Loss of weight**: Percentage Duration

PAST HISTORY

- Co-morbidities: DM, HTN, DLP, CAD, CVA, COPD, BA
- Similar complaints Y / N
- Admissions:
- h/o contact:
- h/o surgery:
- Blood transfusion:
- TB, HTN, DM, other STDs

Drug/Treatment History:

- Drugs used previously:
- Current therapy:

Personal History:

Marital status : Married/Unmarried
Diet : Veg/Mixed
Appetite : Normal/Decreased
Sleep : Normal/Disturbed
Bowel : Normal/Diarrhea/Constipation
Micturition : Normal/Retention/Incontinence
Smoker : Yes/No
Alcoholic : Yes/no
Others :

Family History:

HIV :
Other STDs :

General Physical Examination:

Sensorium
Built
Weight
Posture:
Lymphadenopathy: Y / N
Site:
Size:
No.

Spine:
Gait
Meningism
P__ I__ C__ C__ L__ E__

Discrete/Matted
Soft/Firm/Hard

Vitals

Pulse: RR:
BP: Temp:

SYSTEMIC EXAMINATION:

CNS:
Higher Mental Functions: Normal
Conscious/Unconscious/Drowsy/Stuporous/Delirious
Emotional State: Hostile/Depressed/Euphoric
Memory: Preserved/Affected
Oriented/Disoriented
Speech: Normal/Dysphasia/Dysarthria

Cranial Nerves :

- Olfactory: Normal/Abnormal
- Optic: Normal
  - Visual acuity
  - Field of vision
  - Color vision
  - Fundus
  - Light reflex
  - Accommodation reflex
- Occulomotor: Normal/Abnormal
- Trochlear: Normal/Abnormal
- Abducent: Normal/Abnormal
- Trigeminal: Normal/Abnormal
- Facial:Normal / Abnormal
- Vestibulocochlear:Normal / Abnormal
- Glossopharyngeal: Normal / Abnormal
- Vagus: Normal / Abnormal
- Spinal Accessory: Normal / Abnormal
- Hypoglossal:Normal / Abnormal

Motor system:

RIGHT LEFT

- Nutrition/Bulk
- Tone
- Power
- Co-ordination
- Gait:

Sensorysystem:

- Superficial sensations:
- Deep sensations:
- Cortical sensations:

Superficial reflexes:

- Abdominal:
- Cremasteric:
- Bulbocavernous:
- Anal:
- Plantars:

Deep reflexes:

- Biceps :
- Supinator :
- Triceps :
- Knee :
- Ankle:
  (Absent; 1- Present; 2- Brisk; 3- Very Brisk; 4- Clonus)

Cerebellar Signs:

Other Systems

- RS :
- CVS :
- P/A :

INVESTIGATIONS:

- Hb%:
- TC: ___cells/cumm
- N-___%
- L-___%
- E-___%
- M-___%
- B-___%

- Total lymphocyte count:____cells/cumm
- ESR:
- Urine:
- Stool:
- Absolute CD4 count:
- VDRL

CSF: Cell count and type

- Gram stain
- AFB
- Protein
- Glucose
- Chloride
- Indian ink preparation for Cryptococci RADIOLOGY
- X-ray chest :
- CT SCAN:

DIAGNOSED OPPURTUNISTIC INFECTIONS:

ANNEXURE-II

INFORMED CONSENT

Subject identification number for this study: _____

Title of the project: A study on neurological manifestations of HIV with regard to CD4 count.

Name of the principal investigator: Dr.Sreedevi S

I have received the information sheet on the above study and have read and/or understood the written information.

I have been given the chance to discuss the study and ask questions.

I consent to take part in the study and I am aware that my participation is voluntary.

I understand that I may withdraw at any time without this affecting my future care.

I understand that the information collected about me from my participation in this research and sections of any of my medical notes may be looked at by responsible persons (ethics committee members/ regulatory authorities). I give access to these individuals to have access to my records.

I understand I will receive a copy of the patient information sheet and the informed consent form.

_____ _____

Signature/ Thumb Impression of the subject Date

_____

Printed name of the subject in capitals

_____ _____

Signature/ Thumb Impression of the legally acceptable representative subject Date

The legally acceptable representative signature should be added if the subject is a minor or is unable to sign by themselves. The relationship between the subject and the legally acceptable representative should be stated. The impartial witness signature should be added if the subject be stated. The impartial witness signature should be added if subject/legally acceptable representative us unable to read and write and consent should be obtained in his presence.

_____

Printed name of the legally acceptable representative in capitals

_____

Relationship of the legally acceptable representative to subject in capitals

_____ _____

Signature of the person conducting the informed consent discussion

Date

_____

Printed name of the person conducting the informed consent discussion in capitals

_____ _____

Signature of the impartial witness in capitals

Date

_____

Printed name of the impartial witness in capitals

ANNEXURE-III

MASTERCHART

		HISTORY																	GeNeral Physical ExamiNatioN																			CSF ANalysis									
sl. Nos		Sex	age	Nativity	married	New/old	occupatioN	traNsmissioN	wt loss	fever	headache	ALTS	FND	coNvulsioNs	vertigo/im	craNial N	SENSATION	BEHAVIOUR	h/o ptb	SKIN	caNdid	pallor	clubbiNg	LymphadeNopathy	PULSE/MIN	BPmmhg	TEMP(F)	HMF	CRANIAL Nr l	FUNDUS	MOTOR	SENSORY	REFLEXES	meNiNgism	GAIT	CEREBELLAR	PLANTAR	CD4 /ml l	ProteiN (mg/dL)	SUGAR mg/dl	CELLS /dl	NEUTRO %	LYMPHO %	IIC	CXR	toxoplasma atb	CT/MRI	DIAGNOSIS
1	NAGARAJ	M	38	CBE	Y	O	UL	SE	+	+	-	+	_	_	_	N	N	N	-	N	_	_	_	+	96	110/80	102	DL	N	N	N	C	N	+	N	C	AN	322	94	40	110	10	90	-	HK	Nd	N	TBM
2	GANESH	M	36	CBE	Y	N	PF	SE	_	+	+	+	+	+	_	AN	N	N	-	N	_	_	-	_	88	136/90	101	AN	AN	N	AN	N	D	-	N	N	AN	204	150	40	680	6	94	_	N	Nd	N	TBM
3	DHANAM	F	40	CBE	Y	N	Maid	SE	+	+	_	_	_	+	_	N	N	N	-	N	_	+	-	_	62	130/70	98.6	N	N	N	N	N	N	-	N	N	N	286	88	50	98	5	95	_	RULI	Nd	IE	TBM+PTB
4	SUBRAMONI	M	35	CBE	Y	N	UL	ML	+	+	+	_	_	+	_	N	N	N	-	N	_	+	_	_	104	120/80	100	DR	N	N	N	C	N	+	N	C	AN	84	68	38	16	0	100	_	N	P	REL	TXM
5	SIVAM	M	40	TN	Y	N	UL	SE	_	-	+	+	+	+	_	N	N	N	-	N	_	+	_	_	94	110/80	98.6	AN	N	PE	AN	C	B	C	N	N	C	456	Nd	Nd	Nd	Nd	Nd	Nd	N	Nd	HL	CVA
6	MANICKAM	M	23	CBE	Y	N	SL	SE	+	+	+	-	-	+	_	N	N	N	-	N	+	+	_	_	100	170/100	98 6	N	N	N	N	N	C	-	N	N	N	224	92	50	150	16	84	-	N	Nd	N	TBM
7	SELVAM	M	26	CBE	Y	O	DRIVER	SE	_	+	+	+	_	_	_	N	N	N	-	N	_	+	_	_	98	100/70	101	DR	N	PE	N	C	C	-	N	N	AN	218	110	42	232	6	98	_	N	Nd	N	TBM
8	VINAY	M	35	NI	Y	O	ML	SE	_	+	+	+	_	_	_	N	N	N	-	N	+	+	-	_	90	120/70	98.6	DR	N	N	C	C	N	-	N	N	N	106	130	55	70	0	100	_	LULI	N	REL	TXM
9	KATHIRVEL	M	22	CBE	Y	N	SL	SE	_	+	+	+	_	+	_	N	N	N	-	N	_	_	_	_	80	120/80	102	DR	C	PE	N	C	N	-	N	N	N	268	75	45	92	3	97	_	BNHO	Nd	IE	TBM+PTB
10	PITCHAMAL	F	28	CBE	Y	O	UL	SE	_	+	-	-	+	-	-	AN	AN	N	-	AN	_	_	_	+	120	110/70	100	N	AN	N	N	N	N	-	N	N	N	347	Nd	Nd	Nd	Nd	Nd	Nd	N	Nd	N	BP
11	MEENA	F	32	CBE	Y	N	Maid	ML	_	+	+	+	_	_	_	N	N	N	-	N	_	+	+	_	110	110/80	103	DR	N	N	N	N	C	-	C	AN	AN	202	350	74	252	20	80	_	N	Nd	N	TBM
12	RANGAN	M	36	CBE	Y	O	UL	ML	+	+	+	_	_	_	_	N	N	N	-	N	+	_	_	+	70	110/60	98.6	N	N	C	N	N	N	-	N	N	N	34	112	56	8	0	100	_	N	Nd	CE	BM
13	VELLINGIRI	M	27	TN	Y	O	UL	SE	_	+	+	+	_	+	_	N	N	N	+	N	_	+	-	+	100	130/80	100	S	N	N	N	C	N	+	C	AN	C	282	70	55	155	2	98	_	N	Nd	HC	TBM
14	BABU	M	38	SI	Y	N	UL	SE	_	+	-	+	_	_	+	N	N	N	-	N	+	+	-	_	90	110/70	100	N	N	C	N	N	B	-	N	N	N	306	100	24	84	0	100	-	N	Nd	N	TBM
15	PALANI	M	27	CBE	Y	N	DRIVER	SE	_	-	_	_	+	_	_	N	N	N	-	AN	_	+	_	-	96	162/92	101	N	AN	N	AN	N	B	-	N	N	N	458	52	45	2	0	100	-	N	Nd	HL	CVA
16	KUMARAN	M	35	CBE	Y	N	SL	SE	+	+	_	+	_	_	_	N	N	N	-	N	_	+	_	_	100	100/60	98.6	DR	N	N	N	N	N	C	AN	N	N	106	85	65	400	0	100	_	N	Nd	CE	TBM
17	SABIYAMMAL	F	34	CBE	Y	N	H/W	SE	_	+	_	+	+	_	_	AN	N	N	-	N	_	_	_	-	78	158/94	98.6	N	C	N	AN	N	D	-	N	AN	AN	586	Nd	Nd	Nd	Nd	Nd	Nd	N	Nd	HL	CVA
18	VIJAYA	F	25	CBE	S	N	H/W	U	-	+	+	+	_	_	_	N	N	N	-	N	_	_	_	_	72	120/80	98.6	N	C	C	N	C	N	-	AN	AN	C	58	75	32	768	96	4	-	N	N	REL	TXM
19	CHINAMA	F	33	CBE	Y	O	Maid	SE	+	_	-	_	-	+	_	N	N	N	+	N	_	+	_	_	90	110/70	99	N	N	N	N	N	B	-	N	N	AN	292	95	40	86	6	94	-	0	Nd	N	TBM
20	ARUMUGHAM	M	32	CBE	Y	N	PF	SE	_	_	+	_	+	_	_	N	N	N	-	N	_	+	_	_	90	110/80	98.6	AN	N	N	AN	N	A	-	N	N	N	252	180	40	14	0	100	_	N	Nd	Nd	GBS
21	KANIMOZHI	F	41	CBE	Y	N	UL	SE	_	-	+	_	_	_	_	N	N	N	-	N	_	+	-	_	100	120/80	99.8	N	N	N	N	N	N	+	N	N	N	166	180	20	18	20	61	+	N	Nd	N	CM
22	BALAN	M	40	SI	Y	N	SL	SE	+	-	_	_	+	_	_	N	AN	AN	-	N	_	_	+	_	88	120/70	103	N	N	N	AN	AN	B	-	N	N	C	98	100	72	9	0	100	_	N	Nd	ANM	MLP
23	SATHYA	M	45	CBE	Y	O	DRIVER	SE	_	+	_	_	+	_	+	N	N	N	-	N	+	+	_	_	120	110/70	101	AN	C	N	N	N	N	+	N	N	AN	142	150	80	140	2	98	_	EM	Nd	N	TBM
24	MANICKAM	M	44	CBE	Y	N	UL	SE	_	+	+	+	_	+	_	N	N	N	-	N	_	+	-	_	98	120/70	100	AN	N	N	AN	C	C	-	N	N	N	248	450	72	230	0	100	_	RMZI	Nd	MEL	CTBLM
25	MOORTHY	M	26	CBE	S	O	SL	SE	_	+	_	_	-	+	_	N	N	N	-	N	_	-	_	_	88	120/70	98.6	N	C	C	N	N	N	-	N	N	N	346	112	60	188	4	96	Nd	N	Nd	N	TBM
26	JAMBULINGAM	M	34	TN	Y	O	DRIVER	SE	_	+	+	_	_	_	_	N	N	N	+	N	_	+	-	_	102	120/80	99	N	N	C	N	N	C	-	N	C	C	272	140	68	400	10	90	_	N	Nd	Nd	TBM
27	SANKAR	M	30	TN	S	O	UL	SE	_	+	+	+	_	_	_	N	N	N		N	_	+	-	+	106	120/80	99	N	C	N	N	N	N	-	N	N	N	182	182	34	142	13	87	_	LUZI	Nd	Nd	TBM+PTB
28	RAMAN	M	32	CBE	Y	N	UL	SE	_	+	_	_	1+	_	_	N	N	N		N	_	+	-	+	92	130/00	101	DR	N	N	AN	AN	D	+	N	C	AN	342	332	52	138	0	100	_	N	Nd	N	TBM
29	GOPAL	M	35	CBE	Y	N	SL	SE	_	+	_	+	_	_	_	N	N	N	+	N	_	_	_	_	84	130/00	99	N	N	N	C	N	N	-	N	N	N	206	201	35	236	14	96	_	RUZI	Nd	N	TBM+PTB
30	KANNAN	M	30	SI	Y	O	DRIVER	SE	+	+	-	_	_	+	_	N	N	N	-	N	_	+	-	+	0	110/70	99	N	C	N	AN	N	N	C	N	N	N	34	160	40	52	0	100	_	N	P	REL	TXM
31	JAMBULINGAM	M	35	CBE	Y	O	SL	SE	+	+	_	+	_	_	_	N	N	N	-	N	_	+	_	_	82	140/80	98.6	DR	C	N	N	C	B	-	N	N	AN	206	158	43	148	0	100	_	N	Nd	N	TBM
32	MAHESH	M	28	CBE	S	N	SL	SE	-	+	_	+	_	_	_	N	N	N	-	N	+	+	-	_	98	110/70	100	S	C	PE	N	N	N	+	N	C	N	224	315	20	225	2	98	_	N	Nd	N	TBM
33	VELMURUGAN	M	40	CBE	Y	N	SL	SE	_	+	_	+	+	_	_	N	N	N	+	N	_	+	_	_	88	110/70	100	DR	N	N	AN	AN	B	+	C	N	N	82	135	40	154	0	100	_	N	Nd	SEL	CTBLM
34	NATCHIMUTHU	M	51	TN	Y	N	UL	SE	+	+	+	+	_	+	_	N	N	N	-	N	_	+	+	_	108	130/70	102	DR	N	PE	N	C	B	C	N	C	N	346	98	45	132	0	100	Nd	N	Nd	CE	TBM
35	BABY	F	38	SI	Y	N	PF	SE	-	+	+	_	_	_	+	N	N	N	-	N	+	+	_	_	88	110/70	99	N	N	N	N	N	N	+	N	N	N	41	26	30	180	20	80	_	N	P	REL	TXM
36	PALANISAMY	M	34	CBE	Y	N	DRIVER	SE	-	-	-	+	+	-	-	N	N	N	-	N	_	+	-	_	106	172/94	98.6	DR	N	AN	AN	N	B	-	AN	N	C	384	70	45	2	0	100	Nd	N	Nd	HL	CVA
37	VIVEK	M	32	NI	Y	N	ML	SE	_	+	+	_	+	_	_	N	N	N	-	N	_	-	_	_	78	130/80	101	N	N	N	N	N	N	-	N	N	N	426	150	72	90	20	80	-	N	Nd	N	TBM
38	SELVI	F	44	CBE	Y	N	SL	U	_	+	+	+	_	_	_	N	N	N	-	N	_	-	-	_	84	120/80	98.6	DR	N	AN	N	C	B	+	N	N	C	268	220	45	168	0	100	_	N	Nd	CE	TBM
39	BALAN	M	28	CBE	Y	O	SL	SE	_	+	+	+	_	_	_	N	N	AN	-	N	_	+	_	_	84	100/80	98.6	AN	N	C	N	N	N	-	N	C	N	282	105	48	140	0	100	_	N	Nd	IE	TBM
40	PALANISAMY	M	26	TN	S	O	STUDENT	ML	_	+	+	+	1+	+	-	N	N	N	-	N	+	+	-	_	80	100/60	99	S	N	N	AN	C	B	-	C	N	AN	28	85	33	1300	99	1	_	N	P	REL	TXM
41	KARTHIKEYAN	M	28	CBE	Y	N	STUDENT	SE	_	+	+	-	-	-	-	N		N	-	N	+	+	_	_	80	110/70	100	N	N	N	N	N	N	+	N	N	N	98	105	45	150	0	100	_	N	Nd	N	BM
42	MOHANAMBAL	F	30	CBE	Y	O	Maid	U	_	+	-	-	-	+	-	N		N	-	N	_	+	-	+	84	120/80	98.6	N	N	N	N	N	B	-	N	N	N	352	45	52	90	0	100	_	RUZO	Nd	CE	TBM
43	CHELLADURAI	M	45	CBE	Y	O	UL	SE	_	_	_	+	-	-	_	N	N	N	-	N	_	+	_	+	96	120/80	99	DL	N	PE	N	N	N	+	C	N	N	452	96	50	300	2	98	-	N	Nd	CE	TBM
44	RAJA	M	34	CBE	Y	O	SELF EMPL	SE	+	+	+	+	+	-	_	N	N	N	-	N	_	+	_	_	86	100/70	100	S	N	C	AN	C	B	-	AN	AN	C	224	180	90	138	10	90	_	N	Nd	N	TBM
45	DEVAN	M	42	CBE	Y	N	SELF EMPL	SE	-	+	-	+	-	-	-	N	N	N	-	AN	+	N	_	_	80	120/70	99	N	AN	N	N	N	C	-	N	C	C	374	106	62	326	3	97	-	LUZI	Nd	N	TBM
46	PADMA	F	32	CBE	S	O	UL	SE	+	+	+	-	-	-	-	N	N	N	-	N	-	+	-	-	98	112/82	102	N	N	C	N	C	N	C	N	N	N	88	45	42	52	0	100	+	N	Nd	N	CM
47	SENTHIL	M	26	TN	Y	N	SL	SE	+	+	+	+	-	-	-	N	N	N	+	N	-	-	-	-	106	102/60	101	N	AN	N	N	N	N	-	C	C	N	320	95	48	152	2	98	-	HK	Nd	N	TBM
48	JAGAN	M	28	CBE	Y	N	SL	SE	-	+	-	+	-	-	+	N	N	AN	-	N	-	-	-	-	92	98/62	99	N	N	N	N	N	N	-	N	N	AN	254	102	50	225	3	97	-	N	Nd	CE	TBM
49	KANNAMA	F	22	CBE	Y	O	STUDENT	SE	+	+	-	+	-	-	-	N	N	N	-	N	+	-	+	-	78	128/78	98.6	N	N	AN	AN	N	C	-	C	C	N	208	62	32	1352	97	3	-	N	Nd	N	BM
50	RAVI	M	36	CBE	Y	O	PF	SE	+	-	+	+	-	-	-	N	N	N	-	AN	-	+	-	+	86	136/92	99	S	N	N	N	C	N	+	AN	N	N	256	86	35	233	0	100	-	RULI	Nd	N	TBM+PTB
51	MUTHUCHELVI	F	24	CBE	Y	N	UL	SE	-	-	-	-	+	-	-	N	AN	N	-	N	-	-	-	-	94	118/84	101	N	N	N	N	AN	B	-	N	N	AN	178	Nd	Nd	Nd	Nd	Nd	Nd	N	Nd	ANM	ML
52	ANAND	M	21	TN	Y	N	STUDENT	U	-	+	+	+	+	-	-	N	N	N	-	N	-	+	-	-	108	100/70	99	N	N	C	N	N	N	-	N	C	N	273	121	47	103	0	100	-	HK	Nd	N	TBM
53	NAGAMMA	F	42	TN	Y	N	UL	SE	-	-	-	-	+	+	-	AN	N	N	-	N	-	+	-	-	82	158/88	102	N	AN	PE	AN	N	B	-	N	N	AN	194	56	40	5	100	0	-	N	Nd	HL	CVA
54	LAKSHMI	F	32	CBE	Y	N	SL	SE	-	+	+	+	-	-	-	N	N	N	-	N	-	-	-	+	112	130/80	101	N	N	N	N	N	N	-	N	N	N	252	106	42	222	2	98	-	N	Nd	Nd	TBM
55	ETHIRAJ	M	25	CBE	S	O	SL	SE	+	+	-	+	-	+	-	N	N	N	-	N	-	-	-	-	88	122/84	99	DL	N	AN	N	C	N	-	N	C	N	408	88	50	132	0	100	-	N	Nd	Nd	TBM
56	VENKAT	M	33	CBE	S	N	SL	SE	+	-	+	-	-	-	-	N	N	N	-	N	-	+	-	-	92	110/70	98.6	N	N	N	C	N	N	+	C	N	C	58	62	40	60	0	100	-	N	P	REL	TXM
57	USHA	F	29	CBE	Y	N	H/W	SE	-	+	-	+	-	-	-	AN	N	N	+	N	-	-	-	-	106	124/88	100	N	N	N	N	N	N	-	N	AN	N	150	75	46	99	2	98	-	HK	Nd	Nd	TBM+PTB
58	CHELLADURAI	M	34	TN	S	N	SL	SE	-	-	+	+	-	+	-	N	N	N	-	N	-	-	-	-	98	136/84	99	N	N	C	C	N	N	+	N	AN	N	228	89	43	102	0	100	-	N	Nd	N	TBM
59	PETCHIYAMMAL	F	40	CBE	Y	O	H/W	ML	+	+	+	+	-	_	_	N	N	N	+	N	+	+	-	_	98	172/94	101	DR	AN	N	N	N	N	-	N	C	AN	368	112	60	188	4	96	Nd	N	Nd	N	TBM
60	RANI	F	51	CBE	Y	O	H/W	SE	_	+	-	+	+	_	+	N	N	N	-	N	_	+	_	-	88	130/80	98.6	N	N	N	N	N	N	-	N	N	N	272	140	68	400	10	90	_	N	Nd	Nd	TBM
61	GOVINDAN	M	38	SI	Y	N	SL	SE	_	+	+	+	_	+	_	N	N	N	-	N	+	+	_	_	108	120/80	102	N	N	N	AN	N	B	+	N	N	N	182	182	34	142	13	87	_	N	Nd	Nd	BM
62	AMRITHA	F	34	CBE	Y	N	H/W	SE	_	+	+	+	+	-	_	N	N	N	-	N	_	+	_	-	88	120/80	100	DR	N	N	N	AN	N	-	C	C	N	220	332	52	138	0	100	_	N	Nd	N	TBM
63	NATARAJ	M	32	CBE	Y	N	SL	SE	_	+	+	_	+	_	_	N	N	N	-	N	_	+	_	_	106	120/80	101	S	N	N	C	N	B	-	N	N	AN	282	201	35	236	14	96	_	RUZI	Nd	N	TBM+PTB
64	SELVARAJ	M	44	TN	Y	N	UL	SE	_	+	+	+	_	_	_	N	AN	N	-	N	_	+	_	_	78	130/00	99	DR	N	N	N	N	B	+	N	N	N	34	160	40	52	0	100	_	N	Nd	N	BM
65	REVATHY	F	36	CBE	Y	N	H/W	U	+	+	+	_	-	+	_	AN	N	N	+	N	_	N	_	_	84	130/00	99	DR	AN	N	AN	C	N	-	N	N	AN	368	158	43	148	0	100	_	N	Nd	N	TBM
66	MANI	M	40	CBE	Y	O	DRIVER	SE	_	+	-	+	_	_	_	N	N	N	-	N	_	+	-	_	84	110/70	98.6	N	N	N	C	N	B	+	N	C	N	224	315	20	225	2	98	_	N	Nd	N	TBM
67	JAMUNA	F	35	CBE	Y	N	H/W	SE	_	+	_	+	_	_	_	N	N	N	-	N	_	-	+	_	80	140/80	100	DR	N	N	N	AN	N	+	C	N	AN	206	135	40	154	0	100	_	N	Nd	SEL	CTBLM
68	PALANI	M	40	CBE	S	N	DRIVER	SE	_	+	+	+	1+	_	_	N	N	N	-	N	_	-	_	_	80	120/70	100	N	N	C	N	C	B	-	N	N	N	202	98	45	132	0	100	Nd	N	Nd	CE	TBM
69	VIMALA	F	23	CBE	Y	N	STUDENT	SE	+	+	-	-	_	_	+	N	N	N	-	N	_	-	-	_	84	112/82	102	DR	N	N	N	N	N	-	N	N	AN	41	26	30	180	20	80	_	N	P	REL	TXM
70	MUTHOO	M	26	CBE	Y	O	STUDENT	SE	_	+	+	-	_	_	_	N	N	N	-	N	+	+	_	_	96	102/60	99	AN	N	C	AN	N	B	-	N	C	N	498	70	45	2	0	100	Nd	N	Nd	HL	CVA
71	DHANJAY	M	35	NI	Y	N	ML	SE	-	-	+	+	_	+	_	N	N	N	-	N	_	-	-	_	86	98/62	98.6	S	N	N	C	N	N	-	C	N	N	384	150	72	90	20	80	-	N	Nd	N	TBM
72	PALANIAPPAN	M	22	CBE	Y	O	SL	SE	+	+	-	+	_	_	_	AN	N	N	+	AN	_	+	-	+	80	128/78	101	N	N	C	N	C	B	-	N	C	N	198	220	45	168	0	100	_	N	Nd	CE	TBM
73	KRISHNASAMY	M	28	CBE	Y	O	SL	SE	_	+	-	+	+	_	_	N	N	N		N	_	+	-	+	98	136/92	99 8	N	N	N	N	N	C	-	N	N	N	228	105	48	140	0	100	_	N	Nd	IE	TBM
74	RADHIKA	F	32	TN	Y	O	H/W	SE	_	+	+	-	_	_	_	N	N	N		N	_	-	_	_	106	118/84	103	DL	N	N	AN	C	B	+	C	N	C	28	85	33	1300	99	1	_	HK	P	REL	TXM

KEY TO MASTER CHART

ALTS	Altered sensorium
AN/AbN	Abnormal
ANM	Abnormal MRI
B	Brisk
BM	Bacterial Meningitis
BNHO	Bilateral Nonhomogenous opacity
BP	Bell's Palsy
C	Could Not be tested
CBE	Coimbatore
CE	Cerebral edema
CM	CryptococcalMeningitis
CTBLM	CNS Tuberculoma
CXR	Chest x ray
D	Decreased
DL	Delirious
DR	Drowsy
EM	Emphysematous
F	Female
FND	Focal Neurological deficit
H/W	House wife
HC	Hydrocephalous
Hk	Healed kochs
HL	Hypo denseLesion
HMF	Higher mentalfunctions
IE	Inflammatory Exudate
IIC	IndianInk for Cryptococci
LULI	Left lower lobe infiltrates

LUZI	Left upper zoneinfiltrates
M	Male
MEL	Multiple enhancinglesion
ML	Multiple
ML	Migrant Labourer
MLP	Myelopathy
N	New
N	Negative/Normal
ND	Not done
NI	North Indian
O	Old
P	Positive
PE	Papilledema
REL	Ring enhancing lesion
RMZI	Right middle zone opacity
RS	Respiratory system
RULI	Right upper lobe infiltrates
RUZO	Right upper zone opacity
S	Single
SE	Sexual
SEL	Singleenhancinglesion
SI	South Indian - outside TN
SO	Self-occupation
TN	TamiliaN outside Coimbatore
U	Unknown
Y	Yes